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| <b>(54) Title:</b> PHARMACEUTICAL COMPOSITION CONTAINING ANTIULCER AGENT<br><br><b>(57) Abstract</b><br><br>An enteric pharmaceutical composition, containing antiulcer agent, improved in stability and unchanged in dissolution property with the lapse of time is provided, which comprises a core portion including a 2-[(2-pyridyl)methylsulfinyl] benzimidazole compound that has antiulcer activity and is unstable to acid, an undercoating of one or two layers covering the core portion and an enteric coating further covering the undercoating. The core portion and/or the undercoating comprise a stabilizer selected from the group consisting of aluminum hydroxide-sodium bicarbonate coprecipitate alone, a mixture of the aforementioned coprecipitate and a buffer e.g. disodium hydrogenphosphate. |  |  |

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## DESCRIPTION

## PHARMACEUTICAL COMPOSITION CONTAINING ANTIULCER AGENT

## [Technical Field]

This invention relates to a pharmaceutical composition containing an antiulcer agent, which composition is improved in stability and unchanged in dissolution property with time.

## [Background Art]

2-[(2-Pyridyl)methylsulfinyl] benzimidazole compounds (simply referred to as "benzimidazole compounds") having H<sup>+</sup>-K<sup>+</sup> ATPase inhibitory activity are useful as therapeutic agents for digestive ulcers which serve to suppress potently the secretion of gastric acid. The inhibitory activity is so potent and lasting that they have attracted attention as a next-generation therapeutic agent for digestion ulcers which supersedes histamine H<sub>2</sub> receptor antagonists such as cimetidine, etc. In particular, benzimidazole compounds described in Japanese Patent First Publications [41783/1979, 50978/1986 and 6270/1989 have a potent gastric antiulcer activity and are corroborated to have clinical usefulness.

These benzimidazole compounds disclosed, however, have poor stability. That is, they are unstable, in the solid state, to heat, humidity and light, and are susceptible, in an acidic or neutral aqueous solution, to rapid decomposition and significant coloring. Further, in the form of preparations such as tablets, fine granules, granules, capsules and powders, the benzimidazole compounds are adversely affected by other ingredients than them in the preparations and becomes unstable, thus causing decrease in content thereof and color change with

the lapse of time. Of these preparations, where the tablets or granules are applied with an enteric coating, the compatibility of the compounds with the enteric agent (e.g. cellulose acetate/phthalate, hydroxypropylmethylcellulose phthalate, hydroxymethylcellulose acetate succinate, methacrylic acid/acrylic acid copolymer) is so poor that the decrease in content and coloring occur.

The manufacture of oral preparations of benzimidazole compounds necessitates incorporating another ingredients and applying an enteric coating, but the stability of the compounds is thus adversely affected, and consequently, it has been difficult to manufacture the oral preparations.

In the past, in order to obtain a stable pharmaceutical preparation of benzimidazole compounds having antiulcer activity, there has been proposed a method of bringing the compounds into homogeneous contact with a magnesium and/or calcium salt of basic inorganic acid (e.g. heavy magnesium carbonate, magnesium oxide, precipitated calcium carbonate, calcium hydroxide) (Japanese Patent Publication 38247/1991). According to the Publication 38247/1991, the change of the pharmaceutical preparation during storage in appearance and content (residue rate) was measured and as a result, it is reported that there was no change of appearance and the content was stable. However, we, the inventors have traced the Publication according to its method as described by preparing enteric tablets of omeprazole and conducting stability test, and demonstrated that significant coloration and significant decrease in content have been caused because of the effects of

the enteric coating agent and accordingly, sufficiently stable preparations cannot be obtained.

Again, Japanese Patent First Publication 283964/1987 discloses a composition comprising a benzimidazole derivative and its 5% by weight or more of a basic substance (hydroxides or inorganic acid salts of alkali metals, alkali earth metals or aluminum) and its results of preservation stability (residue amount). However, it will be evident that in case where the composition is covered with an enteric coating agent, stable enteric preparations cannot be likewise obtained for the reasons above.

On the other hand, these problems have been solved by a new pharmaceutical preparation which is disclosed in Japanese Patent First Publication 258320/1987. The new preparation is composed of ① a core portion containing an active component, ② an intermediate coating on the core portion consisting of one or more layers and ③ an enteric coating on the intermediate coating, thereby forming a three-coat oral enteric pharmaceutical preparation, wherein the core portion comprises an alkaline reactive compound, e.g. magnesium oxide, magnesium hydroxide, etc. and the intermediate coating comprises a pH buffering alkaline compound, e.g. magnesium oxide, magnesium hydroxide, or complex compound  $[Al_2O_3 \cdot 6MgO \cdot CO_2 \cdot 12H_2O$  or  $MgO \cdot Al_2O_3 \cdot 2SiO_2 \cdot nH_2O$  ( $n$  is non-integer of less than 2). Thus, the preparation is characterized in that the core portion includes an alkaline reactive compound and the intermediate coating includes a pH buffering alkaline compound. The Applicant of this invention is manufacturing and selling stable

omeprazole preparations wherein magnesium hydroxide is selected as a best alkaline compound and synthetic hydrotalcite, as a pH buffering alkaline compound of the intermediate coating.

However, in the case of the omeprazole preparations in tablet form, problems have occurred in the course of manufacturing process in that since the film formability of the first and second intermediate coating layers is very poor, they cause partial separation and because of brittleness, defective coating films are produced by impact during the manufacturing process, with the result that defective tablets in the intermediate coating coexist. As a consequence, inclusion of reject tablets, which are partially browned because of direct contact of the enteric coating with the core portion, has occurred. Further problem is that the pharmaceutical preparations are unstable to humidity and consequently, when stored under humidifying condition, have caused delay in disintegration of the tablets and impairment of dissolution. Thus the three-coat pharmaceutical preparations are improved in stability; nevertheless, the manufacture of them is likely to produce reject products, and it is a current practice to apply a tight, dampproof package to the tablets for the marketing process, which is not advantageous in economy aspect, as well.

[Disclosure of Invention]

In view of the current situation described above, with a view toward developing more useful preparations of benzimidazole compounds having antiulcer activity and being unstable to acids, a variety of substances have been investigated intensively, and it has been found that the foregoing problems

can be solved by incorporating a stabilizer selected from the group consisting of aluminum hydroxide • sodium bicarbonate coprecipitate alone, a mixture of the aforesaid coprecipitate and a buffer, a mixture of aluminum glycinate and a buffer, a mixture of an amino acid and a buffer a mixture of an acid salt of an amino acid and a buffer or a mixture of an alkali salt of an amino acid and a buffer, which has matured to this invention.

This invention is directed to :

(1) an enteric pharmaceutical composition, containing antiulcer agent, improved in stability and unchanged in dissolution property with the lapse of time, which composition comprises a core portion including a 2-[(2-pyridyl)methylsulfinyl]-benzimidazole compound that has antiulcer activity and is unstable to acid, and undercoating of one or two layers covering the core portion and an enteric coating further covering the undercoating, wherein said core portion and/or said undercoating comprise a stabilizer selected from the group consisting of aluminum hydroxide • sodium bicarbonate coprecipitate alone, a mixture of the aforementioned coprecipitate and a buffer, a mixture of aluminum glycinate and a buffer, a mixture of an amino acid and a buffer, a mixture of an acid salt of an amino acid and a buffer, and a mixture of an alkali salt of an amino acid and a buffer;

(2) an enteric pharmaceutical composition improved in stability and unchanged in dissolution property with the lapse of time, which composition comprises a core portion including a 2-[(2-pyridyl)methylsulfinyl] benzimidazole compound that has antiulcer activity and is unstable to an acid, an undercoating

of one or two layers covering the core portion, and an enteric coating further covering the undercoating, wherein the core portion and/or the undercoating comprise aluminum hydroxide · sodium bicarbonate coprecipitate;

(3) the enteric pharmaceutical composition as set forth in item 2, wherein the aluminum hydroxide · sodium bicarbonate coprecipitate in the undercoating is in the range of 0.01~10 parts by weight based on 100 parts by weight of the core portion;

(4) the enteric pharmaceutical composition as set forth in item 2, wherein the undercoating comprises aluminum hydroxide · sodium bicarbonate coprecipitate and talc;

(5) an enteric pharmaceutical composition improved in stability and unchanged in dissolution property with the lapse of time, which composition comprises a core portion including a 2-[(2-pyridyl)methylsulfinyl] benzimidazole compound that has antiulcer activity and is unstable to an acid, an undercoating of one or two layers covering the core portion, and an enteric coating further covering the undercoating, wherein the core portion and/or the undercoating comprise aluminum hydroxide · sodium bicarbonate coprecipitate and a buffer;

(6) the enteric pharmaceutical composition as set forth in item 5, wherein the aluminum hydroxide · sodium bicarbonate coprecipitate and a buffer are in the range of, respectively, 0.01~0.5 part by weight and 0.01~2 parts by weight based on 1 part by weight of the 2-[(2-pyridyl)methylsulfinyl]-benzimidazole compound;

(7) the enteric pharmaceutical composition as set forth in item



5, wherein the buffer is sodium tartarate, sodium acetate, sodium bicarbonate, sodium carbonate, sodium polyphosphate, potassium polyphosphate, sodium pyrophosphate, potassium pyrophosphate, disodium hydrogenphosphate, dipotassium hydrogenphosphate, trisodium phosphate or tripotassium phosphate;

(8) an enteric pharmaceutical composition improved in stability and unchanged in dissolution property with the lapse of time, which composition comprises a core portion including a 2-[(2-pyridyl)methylsulfinyl] benzimidazole compound that has antiulcer activity and is unstable to an acid, an undercoating of one or two layers covering the core portion, and an enteric coating further covering the undercoating, wherein the core portion and/or the undercoating comprise aluminum glycinate and a buffer;

(9) the enteric pharmaceutical composition as set forth in item 8, wherein the aluminum glycinate and the buffer are in the range of, respectively, 0.1~2 parts by weight and 0.01~2 parts by weight based on 1 part by weight of the 2-[(2-pyridyl)methylsulfinyl] benzimidazole compound;

(10) the enteric pharmaceutical composition as set forth in item 8, wherein the buffer is sodium tartarate, sodium acetate, sodium bicarbonate, sodium carbonate, sodium polyphosphate, potassium polyphosphate, sodium pyrophosphate, potassium pyrophosphate, disodium hydrogenphosphate, dipotassium hydrogenphosphate, trisodium phosphate or tripotassium phosphate;

(11) an enteric pharmaceutical composition improved in stability

and unchanged in dissolution property with the lapse of time, which composition comprises a core portion including a 2-[(2-pyridyl)methylsulfinyl] benzimidazole compound that has antiulcer activity and is unstable to an acid, an undercoating of one or two layers covering the core portion, and an enteric coating further covering the undercoating, wherein the core portion and/or the undercoating comprise a mixture of amino acid, an acid salt of an amino acid or an alkali salt of an amino acid and a buffer;

(12) the enteric pharmaceutical composition as set forth in item 11, wherein the amino acid, acid salt of an amino acid, or alkali salt of an amino acid is in the range of 0.01~2 parts by weight and the buffer is in the range of 0.01~2 parts by weight, respectively, based on 1 part by weight of the 2-[(2-pyridyl)methylsulfinyl] benzimidazole compound;

(13) the enteric pharmaceutical composition as set forth in item 11, wherein the amino acid, acid salt of an amino acid or alkali salt of an amino acid is glycine, glycine hydrochloride, L-alanine, DL-alanine, L-threonin, DL-threonin, L-isoleucine, L-valine, L-phenylalanine, L-glutamic acid, L-glutamic acid hydrochloride, sodium L-glutamate, L-asparagic acid, sodium L-asparaglate, L-lysine or L-lysine-L-glutamate; and the buffer is an alkaline metal salt of phosphoric acid, sodium tartarate, sodium acetate, sodium bicarbonate, sodium polyphosphate, sodium pyrophosphate, potassium metaphosphate, magnesium oxide, magnesium hydroxide, magnesium carbonate, magnesium silicate or calcium carbonate;

(14) the enteric pharmaceutical composition as set forth in item

11, wherein the amino acid, acid salt of an amino acid or alkali salt of an amino acid is glycine, L-alanine, DL-alanine or sodium L-glutamate; and the buffer is disodium hydrogenphosphate.

The 2-[(2-pyridyl)methylsulfinyl] benzimidazole compounds having antiulcer activity and being unstable to acid to be used in this invention are described more specifically in the aforementioned publications. Exemplified are 5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole (omeprazole), 2-[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]-sulfinyl-1H-benzimidazole (lansoprazole), 2-[[4-(3-methoxypropoxy)-3-methyl-2-pyridyl]methylsulfinyl]-1H-benzimidazole, 2-[(3,5-dimethyl-4-methoxy-2-pyridyl)methylsulfinyl]-1H-benzimidazole, 6-methyl-2-[(3-methyl-2-pyridyl)-methylsulfinyl]-1H-benzimidazole-5-methylcarboxylate, 5-methyl-2-[(3,5-dimethyl-2-pyridyl)-methylsulfinyl]-1H-benzimidazole, 2-[(4-methoxy-2-pyridyl)-methylsulfinyl]-5-trifluoromethyl-1H-benzimidazole, 2-[(4-methoxy-3-methyl-2-pyridyl)methylsulfinyl]-5-trifluoromethyl-1H-benzimidazole, 2-[(5-ethyl-4-phenoxy-2-pyridyl)-methylsulfinyl]-5-methoxy-1H-benzimidazole, 5-methoxy-2-[(4-phenoxy-2-pyridyl)methylsulfinyl]-1H-benzimidazole, 2-[(3-methyl-4-(2-(N-benzyl-N-methylamino)ethoxy)-2-pyridyl)-methylsulfinyl]-1H-benzimidazole, 2-[(3-methyl-4-(2-morpholinoethoxy)-2-pyridyl)methylsulfinyl]-1H-benzimidazole or 2-[(3-methyl-4-(2-(1,2,3,4-tetrahydroisoquinoline-2-yl)ethoxy)-2-pyridyl)methylsulfinyl]-1H-benzimidazole. The aforementioned compound as an active component is contained in the core

portion in the range of 1 - 50 mg, preferably 5 - 30 mg.

The pharmaceutical preparations as mentioned in 2, 3, 4 above will be described below in more detail:

The amount of the aluminum hydroxide - sodium bicarbonate coprecipitate to be incorporated for the core portion is preferably in the range of 0.01 to 1 part by weight based on 1 part by weight of the benzimidazole compound, but is not limited to this range. The above-mentioned stabilizer may contain further additives used generally in the preparation of pharmaceutical preparations, such as a vehicle, e.g. lactose, mannitol, corn starch, microcrystalline cellulose, a binder, e.g. hydroxypropylcellulose, a disintegrating agent, e.g. low substituted hydroxypropylcellulose, sodium carboxymethylstarch (tradename of Explotab by Kimura Sangyo), calcium carboxymethylcellulose, a surfactant, e.g. sodium laurylsulfate, Tween 80 (tradename), a lubricant, e.g. magnesium stearate, talc, etc.

In accordance with this invention, the core portion can be obtained by admixing homogeneously a benzimidazole compound, aluminum hydroxide - sodium bicarbonate coprecipitate as a stabilizer and, whenever necessary, additives as mentioned above. In admixing, for example, to a mixture of the benzimidazole compound and the stabilizer may be added the additives, or to a mixture of the benzimidazole compound and the additives may be added the stabilizer. The mixture thus obtained is made into powders according to wet granulating method, and then tableted to give core tablets. Alternatively, the mixture is wet kneaded, subsequently granulated with an

extrusion-granulator, and then made into core granules with the aid of Marumerizer (ex Fuji Powder Co.). This mixing method and method of producing tablets and granules are applicable also to the preparations 5 - 14 which will be described hereinafter.

The pharmaceutical preparations as mentioned in 5, 6, 7 above will be described below:

The amount of the aluminum hydroxide · sodium bicarbonate coprecipitate to be incorporated for the core portion is preferably in the range of 0.01 to 0.5 part by weight based on 1 part by weight of the benzimidazole compound, but is not limited to this range. The above-mentioned stabilizer may contain further additives used generally in the preparation of pharmaceutical preparations, such as a vehicle, e.g. lactose, mannitol, corn starch, microcrystalline cellulose, a binder, e.g. hydroxypropylcellulose, a disintegrating agent, e.g. low substituted hydroxypropylcellulose, sodium carboxymethylstarch (tradename of Exprotab by Kimura Sangyo), calcium carboxymethylcellulose, a surfactant, e.g. sodium laurylsulfate, Tween 80 (tradename), a lubricant, e.g. magnesium stearate, talc, etc. A preferred disintegrating agent is sodium carboxymethylstarch.

In case where the stabilization of the benzimidazole compound is insufficient, depending upon the effects of solution property (pH) of the benzimidazole compound or various additives for pharmaceutical preparations such as vehicle, binder, lubricant, etc., the aluminum hydroxide · sodium bicarbonate coprecipitate can be used in admixture with an water-soluble buffer agent thereby to enhance its stability.

The buffer means a substance added to the coprecipitate to control its pH to 8-9 (weak alkali) and includes, for example, sodium tartarate, sodium acetate, sodium bicarbonate, sodium carbonate, sodium polyphosphate, potassium polyphosphate, dipotassium hydrogenphosphate, sodium pyrophosphate, potassium pyrophosphate, disodium hydrogenphosphate, trisodium phosphate or tripotassium phosphate. The amount of the buffer agent to be added is preferably in the range of 0.01 to 2 parts by weight per 1 part by weight of the benzimidazole compound, but is not limited to this range.

The pharmaceutical preparations as mentioned in 8, 9, 10 above will be described below in more detail:

The buffer to be used in the preparations includes, for example, sodium tartarate, sodium acetate, sodium bicarbonate, sodium carbonate, sodium polyphosphate, dipotassium hydrogenphosphate, sodium pyrophosphate, disodium hydrogenphosphate, trisodium phosphate or tripotassium phosphate, among which disodium hydrogenphosphate is preferred.

The amounts of aluminum glycinate and the buffer are preferably in the range of 0.01~2 parts by weight and 0.01~2 parts by weight, respectively, based on 1 part by weight of the benzimidazole compound.

The stabilizer in this invention may be used together with pharmaceutically acceptable additives, for example, an excipient such as lactose, mannitol, cornstarch, crystalline cellulose, etc.; a binder such as hydroxypropylcellulose, etc.; a disintegrator, e.g. low substituted hydroxypropylcellulose, sodium carboxymethylstarch (tradename: Explotab by Kimura Sangyo

Co.), calcium carboxymethylcellulose,  $\alpha$ -starch, etc.; a surfactant, e.g. sodium laurylsulfate, Tween 80 (tradename), etc.; a lubricant such as magnesium stearate, talc, etc.

The pharmaceutical preparations as mentioned in 11, 12, 13, 14 above will be described below:

The amino acid, acid salt of an amino acid, or alkali salt of an amino acid in this invention include, for example, glycine, glycine hydrochloride, L-alanine, DL-alanine, L-threonine, DL-threonine, L-isoleucine, L-valine, L-phenylalanine, L-glutamic acid, L-glutamic acid hydrochloride, sodium L-glutamate, L-asparagic acid, sodium L-asparaglate, L-lysine or L-lysine-L-glutamate alone or in admixture thereof. Of these compounds, glycine, glycine hydrochloride, L-alanine, DL-alanine or sodium L-glutamate are preferred.

The buffer here means a substance added to the amino acid, etc. to control its pH to 8~9 (weak alkali) and includes, for example, an alkaline metal salt of phosphoric acid (disodium hydrogenphosphate, dipotassium hydrogenphosphate, trisodium phosphate, tripotassium phosphate, sodium dihydrogenphosphate, potassium dihydrogenophosphate, etc.), sodium tartarate, sodium acetate, sodium carbonate, sodium bicarbonate, sodium polyphosphate, sodium pyrophosphate, potassium metaphosphate, magnesium oxide, magnesium hydroxide, magnesium carbonate, magnesium silicate or calcium carbonate. Most preferred is disodium hydrogenphosphate. The amounts of the amino acid or the like and the buffer to be incorporated are preferably in the range of 0.01 ~ 2 parts by weight and 0.01~2 parts by weight, respectively, based on 1 part by weight of the

benzimidazole compound, but are not limited thereto.

The stabilizer in this invention may be used together with pharmaceutically acceptable additives, for example, an excipient such as mannitol, cornstarch, crystalline cellulose, etc.; a binder such as hydroxypropylcellulose, etc.; a disintegrator, e.g. low substituted hydroxypropylcellulose, sodium carboxymethylstarch (tradename: Exprotab by Kimura Sangyo Co.), calcium carboxymethylcellulose, etc.; a surfactant, e.g. sodium laurylsulfate, Tween 80 (tradename), etc.; a lubricant such as magnesium stearate, talc, etc.

Onto the core portion (core tablets, core granules) formed in this manner is covered the undercoating of one or two layers, which may contain aluminum hydroxide · sodium bicarbonate coprecipitate or the coprecipitate and buffer, aluminum glycinate and buffer, etc. as a stabilizer. The undercoating agent includes polymers, preferably, pharmaceutically acceptable water-soluble polymers selected from hydroxypropylmethylcellulose, hydroxypropylcellulose, polyvinylpyrrolidone, gelatine, etc., or saccharides such as purified sucrose, mannitol, lactose, etc. Further, additives such as talc, titanium oxide, light silicic acid anhydride may be added.

The undercoating is preferably composed of two layers. The one undercoating layer on the core portion side comprises aluminum hydroxide · sodium bicarbonate coprecipitate, a polymer or saccharide and additives such as talc, whereas the other undercoating layer on the enteric coating side comprises a polymer or saccharide and, whenever necessary, additives such



as talc. The amount of the stabilizer to be incorporated in the undercoating is preferably in the range of 0.01 to 10 parts by weight based on 100 parts by weight of the core portion, but is not limited to the range.

The intermediate product thus obtained can be covered with an enteric coating to give an enteric pharmaceutical preparation. As the enteric coating there may be mentioned cellulose acetate phthalate, hydroxypropylmethylcellulose phthalate, hydroxymethylcellulose acetate succinate, methacrylic acid/acrylic acid copolymer (tradename : Eudragit), etc., and a plasticizer and a pigment may also be incorporated.

As described above, in the 3-coat pharmaceutical preparation comprising the core portion, undercoating and enteric coating, it is essential to incorporate a stabilizer, namely aluminum hydroxide · sodium bicarbonate coprecipitate, etc. for the core portion and/or the undercoating. If any of the requisites is lacking, the intended preparation cannot be obtained. In the pharmaceutical preparations according to Japanese Patent First Publication 258320/1987, if magnesium hydroxide added to the core portion is incorporated also in the undercoating, the enteric coating will be affected adversely thereby. In order to avoid it, in a best preparation of them, a synthetic hydrotalcite is therefore used for the undercoating.

In contrast, according to this invention, a stabilizer such as aluminum hydroxide · sodium bicarbonate coprecipitate added to the core portion is also incorporated in the undercoating. Thereby, the film formability of the undercoating agent (e.g. hydroxypropylmethylcellulose) is good as compared with that of

the undercoating containing synthetic talcite. By the incorporation of a stabilizer such as aluminum hydroxide · sodium bicarbonate coprecipitate and talc in the undercoating, slip of the undercoating during its manufacture is improved and impact during the manufacture is minimized, whereby the occurrence of deficiency of the film is impeded and no rejects of browned tablets are produced accordingly.

It is thus possible to obtain dosage forms suitable for oral administration, namely enteric tablets, granules and capsules encapsulating therein granules. The pharmaceutical preparations in the dosage forms thus obtained have the following characteristics:

- (1) Even if they are stored under severe conditions for a long period of time, there are seen no impairment in appearance and little decrease in content.
- (2) Under humidification at high temperature, the disintegration property is good and dissolution property is not impaired.
- (3) The film formability of the undercoating is superior. Consequently, reject products in the manufacturing process are decreased, leading to curtailment of cost.
- (4) It is possible to simplify the package of products. A longer stability after seal-opening in pharmacies or else can be ensured.

The pharmaceutical preparations of this invention have good gastric antisecretory activity and antiulcer activity, so that they can be used for the treatment of ulcers of digestive organs, etc. in mammals inclusive of the human.

[Brief Description of Drawings]

Fig. 1 is a graphical representation showing the profile of dissolution of omeprazole tablets obtained in Reference Example 1-1;

Fig. 2 is a graphical representation showing the profile of dissolution of omeprazole tablets of this invention obtained in Example 1-2;

Fig. 3 is another graphical representation showing the profile of dissolution of omeprazole tablets obtained in Reference Example 1-1;

Fig. 4 is another graphical representation showing the profile of dissolution of omeprazole tablets of this invention obtained in Example 1-2;

Fig. 5 is a graphical representation showing appearance change of Samples 4, 5, 6 and 7 in Experimental Example 1-4, when preserved, in terms of  $\Delta E$  value.

Fig. 6 is a graphical representation showing the profile of dissolution of omeprazole tablets of this invention obtained in Example 2-2;

Fig. 7 is another graphical representation showing the profile of dissolution of omeprazole tablets of this invention obtained in Example 2-2;

[Best Mode for Carrying out the Invention]

The invention will be hereinbelow described in more detail by way of reference examples, examples and experimental examples, but should not be construed as limiting to them.

Reference Example 1-1

Enteric tablets were produced by using magnesium hydroxide as a stabilizer for the core portion and synthetic hydrotalcite

as a stabilizer for the undercoating in accordance with the method of Japanese Patent First Publication 258320/1987 as follows:

Tablets (135 mg) containing 20 mg of omeprazole and magnesium hydroxide were formed by means of a rotary tableting machine. The core tablets thus obtained were applied with an undercoating of hydroxypropylmethyl cellulose containing 0.3 mg of synthetic talcite to form a first undercoating layer and further applied with an undercoating solution of hydroxypropylmethyl cellulose to form a second undercoating layer. Then an enteric coating solution containing hydroxypropylmethyl cellulose phthalate was applied onto the second undercoating layer to give enteric tablets.

#### Example 1-1

The composition given below was placed into a kneader to mix it for about 20 minutes and kneaded with an adequate amount of purified water. The mixture was extruded, granulated with a granulating machine (screen diameter of 1.0 mm) and made into spherical granules with Marumerizer (ex Fuji Powder). The granules were dried in a fluidized bed drier at an air supply temperature of 50 °C for 30 minutes and passed through a sieve to give core granules of 14 to 24 meshes.

|  |         |
|--|---------|
| Omeprazole   | 5.0 mg  |
| Aluminum hydroxide · sodium<br>bicarbonate coprecipitate | 5.0 mg  |
| Crystalline cellulose                                    | 4.0 mg  |
| Low substituted hydroxypropylcellulose                   | 4.0 mg  |
| Hydroxypropylcellulose                                   | 0.5 mg  |
| Mannitol   | 56.5 mg |

Total 75.0 mg

The core granules were applied with coatings given below to give enteric granules. The first and second undercoatings were applied in a fluidized spray drier (manufactured by Ohkawara Co.) at an air supply temperature of 75°C and an exhaust temperature of 45°C whereas the enteric coating was applied at an air supply temperature of 65°C and an exhaust temperature of 40°C.

Core granules 75.0 mg

Undercoating 1

|  |           |
|--|-----------|
| Hydroxypropylmethylcellulose                             | 3.5 mg    |
| Aluminum hydroxide • sodium<br>bicarbonate coprecipitate | 1.5 mg    |
| Talc   | 0.5 mg    |
| Purified water   | (64.5 mg) |
| Total  | 5.5 mg    |

Undercoating 2

|                              |           |
|------------------------------|-----------|
| Hydroxypropylmethylcellulose | 3.5 mg    |
| Titanium oxide               | 2.5 mg    |
| Talc                         | 0.5 mg    |
| Purified water               | (64.5 mg) |
| Total                        | 6.5 mg    |

Enteric coating

|  |           |
|--|-----------|
| Hydroxypropylmethylcellulose phthalate | 10.7 mg   |
| Cetanol                                | 0.5 mg    |
| Talc                                   | 1.8 mg    |
| Methylene chloride                     | (33.0 mg) |
| Ethanol                                | (86.0 mg) |
| Purified water                         | (33.0 mg) |

Total 13.0 mg

Example 1-2

Omeprazole, aluminum hydroxide · sodium bicarbonate coprecipitate, lactose, sodium carboxymethylstarch, sodium laurylsulfate and hydroxypropylmethyl cellulose in respective amounts given below were mixed homogeneously, kneaded with an adequate amount of purified water and dried in a fluidized bed drier at an air supply temperature of 50°C for 30 minutes. After granulating, the granules were passed through a screen of 24 meshes and mixed with magnesium stearate. The mixture was tableted with a rotary tableting machine to give tablets (core tablets) each of 135 mg.

|  |          |
|--|----------|
| Omeprazole   | 20.0 mg  |
| Aluminum hydroxide · sodium<br>bicarbonate coprecipitate | 15.0 mg  |
| Lactose  | 91.2 mg  |
| Sodium carboxymethylstarch                               | 7.5 mg   |
| Sodium laurylsulfate                                     | 0.3 mg   |
| Hydroxypropylmethylcellulose                             | 0.5 mg   |
| Magnesium stearate                                       | 0.5 mg   |
| Total  | 135.0 mg |

To the core tablets are applied coatings as given below to give enteric tablets. The first and second undercoatings were applied with Highcoater (by Freund Sangyo) at an air supply temperature of 70°C and an exhaust temperature of 40°C at a pan revolution number of 15 rpm. The enteric coating was applied at an air supply temperature of 55°C and an exhaust temperature of 37°C.

Core tablets 135.0 mg

## Undercoating 1

|  |           |
|--|-----------|
| Hydroxypropylmethylcellulose                             | 1.2 mg    |
| Aluminum hydroxide · sodium<br>bicarbonate coprecipitate | 0.3 mg    |
| Talc   | 0.1 mg    |
| Purified water   | (23.0 mg) |
| Total  | 1.6 mg    |

## Undercoating 2

|                              |           |
|------------------------------|-----------|
| Hydroxypropylmethylcellulose | 3.1 mg    |
| Titanium oxide               | 1.0 mg    |
| Talc                         | 0.1 mg    |
| Purified water               | (56.0 mg) |
| Total                        | 4.2 mg    |

## Enteric coating

|  |           |
|--|-----------|
| Hydroxypropylmethylcellulose phthalate | 2.9 mg    |
| Cetanol                                | 0.1 mg    |
| Talc                                   | 0.2 mg    |
| Ethanol                                | (35.0 mg) |
| Purified water                         | (10.0 mg) |
| Total                                  | 3.2 mg    |
| Aggregate                              | 144.0 mg  |

## Experimental Example 1-1

With the enteric tablets obtained in Reference Example 1-1 and Example 1-2 of this invention, preparation characteristics and preservation stability were examined and yielded the results that there were seen no differences between the both as shown in Tables 1-1 and 1-2.

Table 1-1 Preparation Characteristics

|  | Reference Example 1-1 | Example 1-2 |
|--|-----------------------|-------------|
| Weight (mg)  | 143.0                 | 144.0       |
| Diameter (mm)  | 7.13                  | 7.13        |
| Thickness (mm)   | 3.23                  | 3.24        |
| Hardness (kp)  | 13.0                  | 14.0        |
| Disintegration (The Pharmacopeia of Japan, 12 Ed.)                         |                       |             |
| The 1st fluid  |                       |             |
| (Durability after 2 hr.)   | Compliance            | Compliance  |
| The 2nd fluid  | 4.7 min               | 5.8 min     |
| Dissolution (the 2nd fluid, paddle method, 100 rpm)                        |                       |             |
| 10 min.  | 89.3%                 | 96%         |
| 20 min.  | 100.4%                | 100.3%      |
| Stability against of the 1st fluid (the 1st fluid, paddle method, 100 rpm) |                       |             |
| Residue rate of active   |                       |             |
| ingredient after 2 hr.   | 99.8%                 | 99.8%       |

Table 1-2 Stability

| Preservation Conditions | Reference Example 1-1 |            | Example 1-2 |            |
|-------------------------|-----------------------|------------|-------------|------------|
|                         | Appearance            | Content(%) | Appearance  | Content(%) |
| Initial                 | white                 | 99.7       | white       | 99.7       |
| 40°C, one month         | white                 | 99.3       | white       | 99.6       |
| 40°C, two months        | white                 | 100.0      | white       | 99.5       |
| 60°C, two weeks         | white                 | 99.3       | white       | 99.5       |
| 60°C, one month         | white                 | 99.5       | white       | 99.2       |
| 40°C, 75%RH, two weeks  | white                 | 99.3       | white       | 99.5       |
| 40°C, 75%RH, one month  | white                 | 99.3       | white       | 99.3       |



### Experimental Example 1-2

Enteric tablets of omeprazole obtained in Reference Example 1-1 and Example 1-2 were preserved for two weeks under conditions of 25°C, 85% relative humidity and 40°C, 82% relative humidity and thereafter, dissolution test was carried out to determine dissolution rate in the 2nd fluid (pH : ca. 6.8) according to The Japan Pharmacopoeia. The results obtained are shown in Fig.1 to Fig.4.

As will be apparent from Fig.1 and Fig.3, significant deterioration in dissolution was observed with the enteric tablets in Reference Example 1-1 under reservation at 25°C, 85% RH (Fig.1) and at 40°C, 82% RH (Fig.3). On the other hand, it is evident from Fig.2 and Fig.4 that no reduction in dissolution was observed with the enteric tablets of Example 1-2 even after storage of two weeks at 25°C, 85% RH (Fig.2) and at 40°C, 82% RH (Fig.4)

### Example 1-3

Enteric tablets of omeprazole comprising the following compositions are produced according to the method of Example 1-2.

#### Core tablets

|  |          |
|--|----------|
| Omeprazole   | 20.0 mg  |
| Aluminum hydroxide · sodium<br>bicarbonate coprecipitate | 0.5 mg   |
| Lactose  | 101.0 mg |
| Sodium carboxymethylstarch                               | 7.5 mg   |
| Sodium laurylsulfate                                     | 0.2 mg   |
| Hydroxypropylmethylcellulose                             | 0.3 mg   |
| Magnesium stearate                                       | 0.5 mg   |

|  |           |
|--|-----------|
| Total  | 130.0 mg  |
| Undercoating 1   |           |
| Hydroxypropylmethylcellulose                             | 1.1 mg    |
| Aluminum hydroxide • sodium<br>bicarbonate coprecipitate | 0.2 mg    |
| Talc   | 0.1 mg    |
| Purified water   | (20.0 mg) |
| Total  | 1.4 mg    |
| Undercoating 2   |           |
| Hydroxypropylmethylcellulose                             | 3.0 mg    |
| Titanium oxide   | 0.5 mg    |
| Talc   | 0.1 mg    |
| Purified water   | (45.0 mg) |
| Total  | 3.6 mg    |
| Enteric coating  |           |
| Hydroxypropylmethylcellulose phthalate                   | 2.7 mg    |
| Cetanol  | 0.1 mg    |
| Talc   | 0.2 mg    |
| Ethanol  | (30.0 mg) |
| Purified water   | ( 8.5 mg) |
| Total  | 3.0 mg    |
| Aggregate  | 138.0 mg  |

## Example 1-4

Enteric tablets of omeprazole comprising the compositions given below are produced according to the method of Example 1-2.

## Core tablets

|                             |         |
|-----------------------------|---------|
| Omeprazole                  | 20.0 mg |
| Aluminum hydroxide • sodium |         |

|  |           |
|--|-----------|
| bicarbonate coprecipitate                                | 1.0 mg    |
| Lactose  | 100.5 mg  |
| Sodium carboxymethylstarch                               | 7.5 mg    |
| Sodium laurylsulfate                                     | 0.2 mg    |
| Hydroxypropylmethylcellulose                             | 0.3 mg    |
| Magnesium stearate                                       | 0.5 mg    |
| Total  | 130.0 mg  |
| Undercoating 1   |           |
| Hydroxypropylmethylcellulose                             | 1.0 mg    |
| Aluminum hydroxide - sodium<br>bicarbonate coprecipitate | 0.3 mg    |
| Talc   | 0.2 mg    |
| Purified water   | (20.0 mg) |
| Total  | 1.5 mg    |
| Undercoating 2   |           |
| Hydroxypropylmethylcellulose                             | 2.9 mg    |
| Titanium oxide   | 0.5 mg    |
| Talc   | 0.1 mg    |
| Purified water   | (45.0 mg) |
| Total  | 3.5 mg    |
| Enteric coating  |           |
| Hydroxypropylmethylcellulose phthalate                   | 2.7 mg    |
| Cetanol  | 0.1 mg    |
| Talc   | 0.2 mg    |
| Ethanol  | (30.0 mg) |
| Purified water   | ( 8.5 mg) |
| Total  | 3.0 mg    |
| Aggregate  | 138.0 mg  |
| Example 1-5  |           |

Enteric preparation having the compositions given below is produced according to the method of Example 1-2.

Core tablets

|  |          |
|--|----------|
| Omeprazole   | 20.0 mg  |
| Aluminum hydroxide · sodium<br>bicarbonate coprecipitate | 2.5 mg   |
| Lactose  | 103.8 mg |
| Sodium carboxymethylstarch                               | 7.5 mg   |
| Sodium laurylsulfate                                     | 0.3 mg   |
| Hydroxypropylmethylcellulose                             | 0.4 mg   |
| Magnesium stearate                                       | 0.5 mg   |
| Total  | 135.0 mg |

Undercoating 1

|  |           |
|--|-----------|
| Hydroxypropylmethylcellulose                             | 1.2 mg    |
| Aluminum hydroxide · sodium<br>bicarbonate coprecipitate | 0.3 mg    |
| Talc   | 0.1 mg    |
| Purified water   | (23.0 mg) |
| Total  | 1.6 mg    |

Undercoating 2

|                              |           |
|------------------------------|-----------|
| Hydroxypropylmethylcellulose | 3.1 mg    |
| Titanium oxide               | 1.0 mg    |
| Talc                         | 0.1 mg    |
| Purified water               | (45.0 mg) |
| Total                        | 4.2 mg    |

Enteric coating

|  |        |
|--|--------|
| Hydroxypropylmethylcellulose phthalate | 2.9 mg |
| Cetanol                                | 0.1 mg |
| Talc                                   | 0.2 mg |

|                |           |
|----------------|-----------|
| Ethanol        | (30.0 mg) |
| Purified water | ( 8.5 mg) |
| Total          | 3.2 mg    |
| Aggregate      | 144.0 mg  |

## Example 1-6

Enteric preparation of omeprazole having the compositions given below is produced according to the method of Example 2.

## Core tablets

|  |          |
|--|----------|
| Omeprazole   | 20.0 mg  |
| Aluminum hydroxide · sodium<br>bicarbonate coprecipitate | 2.5 mg   |
| Lactose  | 103.7 mg |
| Sodium carboxymethylstarch                               | 7.5 mg   |
| Sodium laurylsulfate                                     | 0.3 mg   |
| Hydroxypropylmethylcellulose                             | 0.5 mg   |
| Magnesium stearate                                       | 0.5 mg   |
| Total  | 135.0 mg |

## Undercoating 1

|  |           |
|--|-----------|
| Hydroxypropylmethylcellulose                             | 1.2 mg    |
| Aluminum hydroxide · sodium<br>bicarbonate coprecipitate | 0.3 mg    |
| Talc   | 0.1 mg    |
| Purified water   | (20.0 mg) |
| Total  | 1.6 mg    |

## Undercoating 2

|                              |           |
|------------------------------|-----------|
| Hydroxypropylmethylcellulose | 4.65mg    |
| Titanium oxide               | 1.5 mg    |
| Talc                         | 0.15mg    |
| Purified water               | (45.0 mg) |

|  |           |
|--|-----------|
| Total                                  | 6.3 mg    |
| Enteric coating                        |           |
| Hydroxypropylmethylcellulose phthalate | 2.9 mg    |
| Cetanol                                | 0.1 mg    |
| Talc                                   | 0.2 mg    |
| Ethanol                                | (30.0 mg) |
| Purified water                         | ( 8.5 mg) |
| Total                                  | 3.2 mg    |
| Aggregate                              | 146.1 mg  |

## Example 1-7

Enteric preparation of omeprazole having the compositions given below is produced according to the method of Example 1-2.

## Core tablets

|  |          |
|--|----------|
| Omeprazole   | 20.0 mg  |
| Aluminum hydroxide • sodium<br>bicarbonate coprecipitate | 5.0 mg   |
| Lactose  | 101.3 mg |
| Sodium carboxymethylstarch                               | 7.5 mg   |
| Sodium laurylsulfate                                     | 0.3 mg   |
| Hydroxypropylmethylcellulose                             | 0.4 mg   |
| Magnesium stearate                                       | 0.5 mg   |
| Total  | 135.0 mg |

## Undercoating 1

|  |           |
|--|-----------|
| Hydroxypropylmethylcellulose                             | 1.0 mg    |
| Aluminum hydroxide • sodium<br>bicarbonate coprecipitate | 0.6 mg    |
| Talc   | 0.2 mg    |
| Purified water   | (20.0 mg) |
| Total  | 1.8 mg    |

## Undercoating 2

|                              |           |
|------------------------------|-----------|
| Hydroxypropylmethylcellulose | 3.0 mg    |
| Titanium oxide               | 1.5 mg    |
| Talc                         | 0.2 mg    |
| Purified water               | (45.0 mg) |
| Total                        | 4.7 mg    |

## Enteric coating

|  |           |
|--|-----------|
| Hydroxypropylmethylcellulose phthalate | 3.0 mg    |
| Cetanol                                | 0.2 mg    |
| Talc                                   | 0.3 mg    |
| Ethanol                                | (30.0 mg) |
| Purified water                         | ( 8.5 mg) |
| Total                                  | 3.5 mg    |

Aggregate 145.0 mg

With the preparations of Examples 1-3 to 1-7, there was observed little change in appearance with the lapse of time.

## Experimental Example 1-3

Enteric preparation of omeprazole having the compositions below is produced according to the method of Example 1-2.

(Sample 1)

## Core tablets

|  |          |
|--|----------|
| Omeprazole   | 20.0 mg  |
| Aluminum hydroxide . sodium<br>bicarbonate coprecipitate | 2.5 mg   |
| Lactose  | 103.8 mg |
| Sodium carboxymethylstarch                               | 7.5 mg   |
| Sodium laurylsulfate                                     | 0.3 mg   |
| Hydroxypropylmethylcellulose                             | 0.4 mg   |
| Magnesium stearate                                       | 0.5 mg   |

|  |           |
|--|-----------|
| Total  | 135.0 mg  |
| Undercoating 1   |           |
| Hydroxypropylmethylcellulose                             | 1.0 mg    |
| Aluminum hydroxide • sodium<br>bicarbonate coprecipitate | 0.3 mg    |
| Talc   | 0.2 mg    |
| Purified water   | (20.0 mg) |
| Total  | 1.5 mg    |
| Undercoating 2   |           |
| Hydroxypropylmethylcellulose                             | 2.9 mg    |
| Talc   | 0.1 mg    |
| Purified water   | (45.0 mg) |
| Total  | 3.0 mg    |
| Enteric coating  |           |
| Hydroxypropylmethylcellulose phthalate                   | 2.7 mg    |
| Cetanol  | 0.1 mg    |
| Talc   | 0.2 mg    |
| Ethanol  | (30.0 mg) |
| Purified water   | ( 8.5 mg) |
| Total  | 3.0 mg    |
| Aggregate  | 142.5 mg  |

Enteric preparation of omeprazole having the compositions given below is produced according to the method of Example 1-2.

(Sample 2)

Core tablets

|  |          |
|--|----------|
| Omeprazole   | 20.0 mg  |
| Aluminum hydroxide • sodium<br>bicarbonate coprecipitate | 2.5 mg   |
| Lactose  | 103.8 mg |



|                              |          |
|------------------------------|----------|
| Sodium carboxymethylstarch   | 7.5 mg   |
| Sodium laurylsulfate         | 0.3 mg   |
| Hydroxypropylmethylcellulose | 0.4 mg   |
| Magnesium stearate           | 0.5 mg   |
| Total                        | 135.0 mg |

## Undercoating 1

|  |           |
|--|-----------|
| Hydroxypropylmethylcellulose                             | 1.0 mg    |
| Aluminum hydroxide · sodium<br>bicarbonate coprecipitate | 0.6 mg    |
| Talc   | 0.2 mg    |
| Purified water   | (20.0 mg) |
| Total  | 1.8 mg    |

## Undercoating 2

|                              |           |
|------------------------------|-----------|
| Hydroxypropylmethylcellulose | 2.6 mg    |
| Talc                         | 0.1 mg    |
| Purified water               | (45.0 mg) |
| Total                        | 2.7 mg    |

## Enteric coating

|  |           |
|--|-----------|
| Hydroxypropylmethylcellulose phthalate | 2.7 mg    |
| Cetanol                                | 0.1 mg    |
| Talc                                   | 0.2 mg    |
| Ethanol                                | (30.0 mg) |
| Purified water                         | ( 8.5 mg) |
| Total                                  | 3.0 mg    |

Aggregate 142.5 mg

Enteric preparation of omeprazole having the compositions  
given below is produced according to the method of Example 1-2.

(Sample 3)

Core tablets

|  |           |
|--|-----------|
| Omeprazole   | 20.0 mg   |
| Aluminum hydroxide•sodium<br>bicarbonate coprecipitate | 2.5 mg    |
| Lactose  | 103.8 mg  |
| Sodium carboxymethylstarch                             | 7.5 mg    |
| Sodium laurylsulfate                                   | 0.3 mg    |
| Hydroxypropylmethylcellulose                           | 0.4 mg    |
| Magnesium stearate                                     | 0.5 mg    |
| Total  | 135.0 mg  |
| Undercoating 1   |           |
| Hydroxypropylmethylcellulose                           | 1.0 mg    |
| Synthetic hydrotalcite                                 | 0.3 mg    |
| Talc   | 0.2 mg    |
| Purified water   | (20.0 mg) |
| Total  | 1.5 mg    |
| Undercoating 2   |           |
| Hydroxypropylmethylcellulose                           | 2.9 mg    |
| Talc   | 0.1 mg    |
| Purified water   | (45.0 mg) |
| Total  | 3.0 mg    |
| Enteric coating  |           |
| Hydroxypropylmethylcellulose phthalate                 | 2.7 mg    |
| Cetanol  | 0.1 mg    |
| Talc   | 0.2 mg    |
| Ethanol  | (3.0 mg)  |
| Purified water   | ( 8.5 mg) |
| Total  | 3.0 mg    |
|  | 142.5 mg  |

The preparations of Sample 1 to Sample 3 were preserved for

2 weeks and 1 month under the conditions of 40°C, 82% RH, and thereafter, change in appearance of them was measured with a colorimeter to determine  $\Delta E$  values of them. The results obtained are shown in Table 1-3.

Table 1-3

| Preparation | 40°C, 82% RH             |                          |
|-------------|--------------------------|--------------------------|
|             | $\Delta E$ after 2 weeks | $\Delta E$ after 1 month |
| Sample 1    | 2.3                      | 5.5                      |
| Sample 2    | 2.4                      | 5.9                      |
| Sample 3    | 3.9                      | 7.7                      |

The preparations (Samples 1, 2) incorporating aluminum hydroxide-sodium bicarbonate coprecipitate in Undercoating 1 were more stable than the preparation (Sample 3) incorporating synthetic talcite in Undercoating 1.

#### Reference Example 1-2

Enteric tablets of lansoprazole of the following composition are produced according to the method of Reference Example 1-1.

#### Core tablets

|                            |          |
|----------------------------|----------|
| Lansoprazole               | 20.0 mg  |
| Magnesium hydroxide        | 10.0 mg  |
| Lactose                    | 73.5 mg  |
| Sodium carboxymethylstarch | 5.0 mg   |
| Sodium laurylsulfate       | 0.2 mg   |
| Hydroxypropylcellulose     | 0.8 mg   |
| Magnesium stearate         | 0.5 mg   |
| Total                      | 110.0 mg |

#### Undercoating 1

|                              |           |
|------------------------------|-----------|
| Hydroxypropylmethylcellulose | 1.0 mg    |
| Synthetic hydrotalcite       | 0.2 mg    |
| Talc                         | 0.1 mg    |
| Purified water               | (20.0 mg) |
| Total                        | 1.3 mg    |

## Undercoating 2

|                              |           |
|------------------------------|-----------|
| Hydroxypropylmethylcellulose | 2.6 mg    |
| Titanium oxide               | 0.8 mg    |
| Talc                         | 0.1 mg    |
| Purified water               | (45.0 mg) |
| Total                        | 3.5 mg    |

## Enteric coating

|  |           |
|--|-----------|
| Hydroxypropylmethylcellulose phthalate | 2.5 mg    |
| Cetanol                                | 0.1 mg    |
| Talc                                   | 0.1 mg    |
| Ethanol                                | (30.0 mg) |
| Purified water                         | ( 8.5 mg) |
| Total                                  | 2.7 mg    |

Aggregate 117.5 mg

## Reference Example 1-3

Enteric tablets of 2-[(3,5-dimethyl-4-methoxy-2-pyridyl)-methylsulfinyl]-1H-benzimidazol (designated as Compound 1) comprising the following compositions are produced according to the method of Reference Example 1-1.

## Core tablets

|                     |         |
|---------------------|---------|
| Compound 1          | 20.0 mg |
| Magnesium hydroxide | 20.0 mg |
| Lactose             | 31.0 mg |

|  |         |
|--|---------|
| Low substituted hydroxypropylcellulose | 8.0 mg  |
| Hydroxypropylmethylcellulose           | 0.7 mg  |
| Magnesium stearate                     | 0.3 mg  |
| Total                                  | 80.0 mg |

## Undercoating 1

|                              |           |
|------------------------------|-----------|
| Hydroxypropylmethylcellulose | 0.8 mg    |
| Synthetic hydrotalcite       | 0.15mg    |
| Talc                         | 0.05mg    |
| Purified water               | (20.0 mg) |
| Total                        | 1.0 mg    |

## Undercoating 2

|                              |           |
|------------------------------|-----------|
| Hydroxypropylmethylcellulose | 2.4 mg    |
| Talc                         | 0.1 mg    |
| Purified water               | (45.0 mg) |
| Total                        | 2.5 mg    |

## Enteric coating

|                              |           |
|------------------------------|-----------|
| Hydroxypropylmethylcellulose | 2.0 mg    |
| Cetanol                      | 0.8 mg    |
| Talc                         | 0.7 mg    |
| Ethanol                      | (30.0 mg) |
| Purified water               | ( 8.5 mg) |
| Total                        | 3.5 mg    |

Aggregate 87.0 mg

Enteric tablets are produced similarly by using 2-[(4-(3-methoxypropoxy)-3-methyl-2-pyridyl)methylsulfinyl]-1H-benzimidazole (designated as Compound 2) instead of Compound 1.  
Example 1-8.

Enteric tablets of lansoprazole having the compositions

below are produced according to the method of Example 1-2.

Core portion

|  |          |
|--|----------|
| Lansoprazole   | 20.0 mg  |
| Aluminum hydroxide-sodium<br>bicarbonate coprecipitate | 10.0 mg  |
| Lactose  | 73.5 mg  |
| Sodium carboxymethylstarch                             | 5.0 mg   |
| Sodium laurylsulfate                                   | 0.2 mg   |
| Hydroxypropylmethylcellulose                           | 0.8 mg   |
| Magnesium stearate                                     | 0.5 mg   |
| Total  | 110.0 mg |

Undercoating 1

|  |           |
|--|-----------|
| Hydroxypropylmethylcellulose                           | 1.0 mg    |
| Aluminum hydroxide-sodium<br>bicarbonate coprecipitate | 0.2 mg    |
| Talc   | 0.1 mg    |
| Purified water   | (20.0 mg) |
| Total  | 1.3 mg    |

Undercoating 2

|                              |           |
|------------------------------|-----------|
| Hydroxypropylmethylcellulose | 2.6 mg    |
| Titanium oxide               | 0.8 mg    |
| Talc                         | 0.1 mg    |
| Purified water               | (45.0 mg) |
| Total                        | 3.5 mg    |

Enteric coating

|  |           |
|--|-----------|
| Hydroxypropylmethylcellulose phthalate | 2.5 mg    |
| Cetanol                                | 0.1 mg    |
| Talc                                   | 0.1 mg    |
| Ethanol                                | (30.0 mg) |

|                |           |
|----------------|-----------|
| Purified water | ( 8.5 mg) |
| Total          | 2.7 mg    |
| Aggregate      | 117.5 mg  |

## Experimental Example 1-4

Enteric preparation of lansoprazole having the compositions given below is produced according to the method of Example 1-2.

## (Sample 4)

## Core tablets

|                              |          |
|------------------------------|----------|
| Lansoprazole                 | 20.0 mg  |
| Lactose                      | 106.0 mg |
| Sodium carboxymethylstarch   | 7.5 mg   |
| Hydroxypropylmethylcellulose | 1.0 mg   |
| Magnesium stearate           | 0.5 mg   |
| Total                        | 135.0 mg |

## Undercoating 1

|  |           |
|--|-----------|
| Hydroxypropylmethylcellulose                           | 1.0 mg    |
| Aluminum hydroxide-sodium<br>bicarbonate coprecipitate | 0.2 mg    |
| Talc   | 0.1 mg    |
| Purified water   | (20.0 mg) |
| Total  | 1.3 mg    |

## Undercoating 2

|                              |           |
|------------------------------|-----------|
| Hydroxypropylmethylcellulose | 2.6 mg    |
| Talc                         | 0.1 mg    |
| Purified water               | (45.0 mg) |
| Total                        | 2.7 mg    |

## Enteric coating

|  |        |
|--|--------|
| Hydroxypropylmethylcellulose phthalate | 2.5 mg |
| Cetanol                                | 0.1 mg |

|                |           |
|----------------|-----------|
| Talc           | 0.1 mg    |
| Ethanol        | (30.0 mg) |
| Purified water | ( 8.5 mg) |
| Total          | 2.7 mg    |
| Aggregate      | 141.7 mg  |

Enteric preparation of lansoprazole having the compositions given below is produced according to the method of Example 1-2.

(Sample 5)

Core tablets

|  |          |
|--|----------|
| Lansoprazole   | 20.0 mg  |
| Aluminum hydroxide-sodium<br>bicarbonate coprecipitate | 1.0 mg   |
| Lactose  | 105.0 mg |
| Sodium carboxymethylstarch                             | 7.5 mg   |
| Hydroxypropylcellulose                                 | 1.0 mg   |
| Magnesium stearate                                     | 0.5 mg   |
| Total  | 135.0 mg |

Undercoating 1

|  |           |
|--|-----------|
| Hydroxypropylmethylcellulose                           | 1.0 mg    |
| Aluminum hydroxide-sodium<br>bicarbonate coprecipitate | 0.2 mg    |
| Talc   | 0.1 mg    |
| Purified water   | (20.0 mg) |
| Total  | 1.3 mg    |

Undercoating 2

|                              |           |
|------------------------------|-----------|
| Hydroxypropylmethylcellulose | 2.6 mg    |
| Talc                         | 0.1 mg    |
| Purified water               | (45.0 mg) |
| Total                        | 2.7 mg    |



## Enteric coating

|  |           |
|--|-----------|
| Hydroxypropylmethylcellulose phthalate | 2.5 mg    |
| Cetanol                                | 0.1 mg    |
| Talc                                   | 0.1 mg    |
| Ethanol                                | (30.0 mg) |
| Purified water                         | ( 8.5 mg) |
| Total                                  | 2.7 mg    |
| Aggregate                              | 141.7 mg  |

Enteric preparation of lansoprazole having the compositions given below is produced according to the method of Example 1-2.

(Sample 6)

## Core tablets

|  |          |
|--|----------|
| Lansoprazole   | 20.0 mg  |
| Aluminum hydroxide-sodium<br>bicarbonate coprecipitate | 5.0 mg   |
| Lactose  | 101.0 mg |
| Sodium carboxymethylstarch                             | 7.5 mg   |
| Hydroxypropylmethylcellulose                           | 1.0 mg   |
| Magnesium stearate                                     | 0.5 mg   |
| Total  | 135.0 mg |

## Undercoating 1

|  |           |
|--|-----------|
| Hydroxypropylmethylcellulose                           | 1.0 mg    |
| Aluminum hydroxide-sodium<br>bicarbonate coprecipitate | 0.2 mg    |
| Talc   | 0.1 mg    |
| Purified water   | (20.0 mg) |
| Total  | 1.3 mg    |

## Undercoating 2

|                              |        |
|------------------------------|--------|
| Hydroxypropylmethylcellulose | 2.6 mg |
|------------------------------|--------|

|  |           |
|--|-----------|
| Talc                                   | 0.1 mg    |
| Purified water                         | (45.0 mg) |
| Total                                  | 2.7 mg    |
| Enteric coating                        |           |
| Hydroxypropylmethylcellulose phthalate | 2.5 mg    |
| Cetanol                                | 0.1 mg    |
| Talc                                   | 0.1 mg    |
| Ethanol                                | (30.0 mg) |
| Purified water                         | ( 8.5 mg) |
| Total                                  | 2.7 mg    |
| Aggregate                              | 141.7 mg  |

Enteric preparation of lansoprazole having the compositions given below is produced according to the method of Example 1-2.

(Sample 7)

Core tablets

|  |          |
|--|----------|
| Lansoprazole   | 20.0 mg  |
| Aluminum hydroxide-sodium<br>bicarbonate coprecipitate | 15.0 mg  |
| Lactose  | 91.0 mg  |
| Sodium carboxymethylstarch                             | 7.5 mg   |
| Hydroxypropylcellulose                                 | 1.0 mg   |
| Magnesium stearate                                     | 0.5 mg   |
| Total  | 135.0 mg |

Undercoating 1

|  |           |
|--|-----------|
| Hydroxypropylmethylcellulose                           | 1.0 mg    |
| Aluminum hydroxide-sodium<br>bicarbonate coprecipitate | 0.2 mg    |
| Talc   | 0.1 mg    |
| Purified water   | (20.0 mg) |

|  |           |
|--|-----------|
| Total                                  | 1.3 mg    |
| Undercoating 2                         |           |
| Hydroxypropylmethylcellulose           | 2.6 mg    |
| Talc                                   | 0.1 mg    |
| Purified water                         | (45.0 mg) |
| Total                                  | 2.7 mg    |
| Enteric coating                        |           |
| Hydroxypropylmethylcellulose phthalate | 2.5 mg    |
| Cetanol                                | 0.1 mg    |
| Talc                                   | 0.1 mg    |
| Ethanol                                | (30.0 mg) |
| Purified water                         | ( 8.5 mg) |
| Total                                  | 2.7 mg    |
| Aggregate                              | 141.7 mg  |

The preparations of Samples 4 to 7 were preserved for 2 and 4 weeks under the conditions of 40°C, 75% RH and thereafter, change in appearance of them was measured with a colorimeter to determine  $\Delta E$  values of them. The results obtained are given in Table 1-4 and Fig. 5.

Table 1-4

| Preparation | 40°C, 75% RH  |               |
|-------------|---------------|---------------|
|             | $\Delta E$    |               |
|             | after 2 weeks | after 4 weeks |
| Sample 4    | 5.1           | 6.6           |
| Sample 5    | 2.6           | 3.7           |
| Sample 6    | 3.1           | 4.0           |
| Sample 7    | 2.7           | 3.6           |

It was proved that the preparations of Samples 5, 6, 7 incorporating aluminum hydroxide-sodium bicarbonate coprecipitate in core tablets have a smaller  $\Delta E$  value and lower appearance change as compared with the preparation of Sample 4 not incorporating the coprecipitate.

#### Example 1-9

Enteric tablets of 2-[(3,5-dimethyl-4-methoxy-2-pyridyl)-methylsulfinyl]-1H-benzimidazole (Compound 1) are produced according to the method of Example 2.

#### Core tablets

|  |         |
|--|---------|
| Compound 1   | 20.0 mg |
| Aluminum hydroxide-sodium<br>bicarbonate coprecipitate | 20.0 mg |
| Lactose  | 31.0 mg |
| Low substituted Hydroxypropylcellulose                 | 8.0 mg  |
| Hydroxypropylmethylcellulose                           | 0.7 mg  |
| Magnesium stearate                                     | 0.3 mg  |
| Total  | 80.0 mg |

#### Undercoating 1

|  |           |
|--|-----------|
| Hydroxypropylmethylcellulose                           | 0.8 mg    |
| Aluminum hydroxide-sodium<br>bicarbonate coprecipitate | 0.15mg    |
| Talc   | 0.05mg    |
| Purified water   | (20.0 mg) |
| Total  | 1.0 mg    |

#### Undercoating 2

|                              |           |
|------------------------------|-----------|
| Hydroxypropylmethylcellulose | 2.4 mg    |
| Talc                         | 0.1 mg    |
| Purified water               | (45.0 mg) |

|  |           |
|--|-----------|
| Total                                  | 2.5 mg    |
| Enteric coating                        |           |
| Hydroxypropylmethylcellulose phthalate | 2.0 mg    |
| Cetanol                                | 0.8 mg    |
| Talc                                   | 0.7 mg    |
| Ethanol                                | (30.0 mg) |
| Purified water                         | ( 8.5 mg) |
| Total                                  | 3.5 mg    |
| Aggregate                              | 87.0 mg   |

Enteric tablets of 2-[[4-(3-methoxypropoxy)-3-methyl-2-pyridyl]methylsulfinyl]-1H-benzimidazole (Compound 2) are similarly produced except that Compound 2 is used instead of Compound 1.

#### Experimental Example 1-5

Similar tests to Experimental Examples 1-1, 1-2 are performed with the enteric tablets obtained in Reference Example 1-2 and Example 1-8 and the enteric tablets of Compound 1 and Compound 2 obtained in Reference Example 1-3 and Example 1-9, and as a result, a good preservation stability and an improved dissolution characteristic are attained with all the tablets.

#### Example 1-10

Core tablets of omeprazole having the following composition were produced by wet granulating method according to Example 1-2 by the use of aluminum hydroxide-sodium bicarbonate coprecipitate as a stabilizer.

#### Core tablets

|            |         |
|------------|---------|
| Omeprazole | 20.0 mg |
|------------|---------|

|  |          |
|--|----------|
| Aluminum hydroxide-sodium<br>bicarbonate coprecipitate | 10.0 mg  |
| Lactose  | 95.7 mg  |
| Sodium carboxymethylstarch                             | 7.5 mg   |
| Sodium laurylsulfate                                   | 0.3 mg   |
| Hydroxypropylmethylcellulose                           | 1.0 mg   |
| Magnesium stearate                                     | 0.5 mg   |
| Total  | 135.0 mg |

Onto the core tablets, Undercoating 1, Undercoating 2 and Enteric coating having the compositions given below were applied according to Example 1-2.

Undercoating 1

|  |           |
|--|-----------|
| Hydroxypropylmethylcellulose                           | 1.2 mg    |
| Aluminum hydroxide-sodium<br>bicarbonate coprecipitate | 0.3 mg    |
| Talc   | 0.1 mg    |
| Purified water   | (23.0 mg) |
| Total  | 1.6 mg    |

Undercoating 2

|                              |           |
|------------------------------|-----------|
| Hydroxypropylmethylcellulose | 3.1 mg    |
| Titanium oxide               | 1.0 mg    |
| Talc                         | 0.1 mg    |
| Purified water               | (56.0 mg) |
| Total                        | 4.2 mg    |

Enteric coating

|  |           |
|--|-----------|
| Hydroxypropylmethylcellulose phthalate | 2.9 mg    |
| Cetanol                                | 0.1 mg    |
| Talc                                   | 0.2 mg    |
| Ethanol                                | (35.0 mg) |

|                |           |
|----------------|-----------|
| Purified water | (10.0 mg) |
| Total          | 3.2 mg    |
| Aggregate      | 144.0 mg  |

On the other hand, core tablets were similarly produced by wet granulating method except that magnesium hydroxide, magnesium oxide or calcium hydroxide was used instead of aluminum hydroxide-sodium bicarbonate coprecipitate, and then similarly applied with film coatings to give enteric tablets.

The enteric tablets thus obtained were preserved for 1 week at 50°C, 75% RH or for 2 weeks at 40°C, 75% RH and thereafter, determined of disintegration time according to the test of the Pharmacopoeia of Japan with the 2nd fluid without using the auxiliary disk. The results obtained are shown in Table 1-5.

Table 1-5

| Stabilizer     |   | Disintegration Time (min.) |                      |                       |
|----------------|---|----------------------------|----------------------|-----------------------|
|                |   | Initial value              | 50°C, 75% RH, 1 Week | 40°C, 75% RH, 2 Weeks |
| This Invention | Aluminum hydroxide-sodium bicarbonate coprecipitate | 4.0                        | 3.5                  | 3.9                   |
| Control        | Magnesium hydroxide                                 | 3.0                        | 29.0                 | 7.5                   |
| do.            | Magnesium oxide                                     | 25.0                       | >30                  | >30                   |
| do.            | Calcium hydroxide                                   | 20.0                       | 22.0                 | >30                   |

The enteric tablets of this invention using aluminum hydroxide-sodium bicarbonate coprecipitate exhibited good disintegration property immediately after preparation (at initial stage) and during preservation in a high temperature, humidified condition. In contrast, those of magnesium hydroxide were deteriorated significantly under humidification

at high temperature. The enteric tablets using magnesium oxide and calcium hydroxide, respectively, were poor in disintegration property from the initial stage thereof as prepared.

#### Example 2-1

The composition given below was placed in a kneader and mixed for about 20 minutes, and kneaded together by adding an appropriate amount of purified water. After granulation with an extrusion-granulator (screen diameter: 1.0 mm), the granules were made into spherical granules with Marumerizer (manufactured by Fujl Powdal). The granules were dried in a fluidized drier at 50 °C for 30 min. and passed through a sieve of 14 to 24 meshes to give core granules.

|   |         |
|---|---------|
| Omeprazole  | 5.0 mg  |
| Aluminum hydroxide-sodium<br>bicarbonate coprecipitate                      | 5.0 mg  |
| Trisodium phosphate ( $\text{Na}_3\text{PO}_4 \cdot 12\text{H}_2\text{O}$ ) | 0.5 mg  |
| Crystalline cellulose   | 4.0 mg  |
| Low substituted hydroxypropylcellulose                                      | 4.0 mg  |
| Hydroxypropylcellulose  | 0.5 mg  |
| Mannitol  | 56.0 mg |
| Total   | 75.0 mg |

The coatings given below were applied onto the core granules thus obtained to give enteric granules. Undercoating 1 and Undercoating 2 were applied in a fluidized spray drier (manufactured by Ohkawara) at an air supply temperature of 75°C and an exhaust temperature of 45°C; and the enteric coating was applied at an air supply temperature of 65°C and an exhaust temperature of 40°C.



|  |           |
|--|-----------|
| Core granules  | 75.0 mg   |
| Undercoating 1   |           |
| Hydroxypropylmethylcellulose                           | 3.5 mg    |
| Aluminum hydroxide-sodium<br>bicarbonate coprecipitate | 1.5 mg    |
| Talc   | 0.5 mg    |
| Purified water   | (64.5 mg) |
| Total  | 5.5 mg    |
| Undercoating 2   |           |
| Hydroxypropylmethylcellulose                           | 3.5 mg    |
| Titanium oxide   | 2.5 mg    |
| Talc   | 0.5 mg    |
| Purified water   | (64.5 mg) |
| Total  | 6.5 mg    |
| Enteric coating  |           |
| Hydroxypropylmethylcellulose phthalate                 | 10.7 mg   |
| Cetanol  | 0.5 mg    |
| Talc   | 1.8 mg    |
| Methylene chloride                                     | (33.0 mg) |
| Ethanol  | (86.0 mg) |
| Purified water   | (33.0 mg) |
| Total  | 13.0 mg   |

## Reference example 2-1

Core granules were produced in a similar procedure to Example 2-1 except that mannitol was used instead of aluminum hydroxide-sodium bicarbonate coprecipitate and trisodium phosphate. Then, coatings similar to Example 2-1 except that talc was additionally incorporated instead of the aluminum hydroxide-sodium bicarbonate coprecipitate in Undercoating 1

were applied to yield enteric granules of omeprazole.

#### Experimental Example 2-1

The enteric granules of omeprazole obtained in Example 2-1 and Reference Example 2-1 were placed in a glass bottle and preserved sealingly at 60°C or under open condition of 75% RH at 40°C for 2 weeks. The change in appearance is shown in Table 2-1.

Table 2-1

|                | At the start | 60°C sealed | 40°C, 75% RH<br>open |
|----------------|--------------|-------------|----------------------|
| Example 6      | white        | white       | white                |
| Ref. Example 4 | pale brown   | brown       | brown                |

As will be apparent from Table 2-1, the enteric granules, which contain aluminum hydroxide-sodium bicarbonate coprecipitate and the buffer agent in the core granules aluminum hydroxide-sodium bicarbonate coprecipitate in the undercoating layer, showed no change in appearance even under severe conditions.

#### Example 2-2

Of the composition given below, aluminum hydroxide-sodium bicarbonate coprecipitate, lactose, sodium carboxymethylstarch, sodium laurylsulfate and hydroxypropylcellulose were mixed homogeneously, and an appropriate amount of purified water dissolving therein sodium pyrophosphate was added. The mixture was kneaded and dried in a fluidized bed drier at 50°C for 30 minutes. The dried powders were passed through a sieve of 24 meshes, and magnesium stearate was further added thereto and mixed. Then, the mixture was made into tablets (core tablets)

each of 135 mg with a rotary tableting machine.

|  |          |
|--|----------|
| Omeprazole   | 20.0 mg  |
| Aluminum hydroxide-sodium<br>bicarbonate coprecipitate | 20.0 mg  |
| Sodium pyrophosphate                                   | 2.0 mg   |
| Lactose  | 83.2 mg  |
| Sodium carboxymethylstarch                             | 8.0 mg   |
| Sodium laurylsulfate                                   | 0.3 mg   |
| Hydroxypropylcellulose                                 | 1.0 mg   |
| Magnesium stearate                                     | 0.5 mg   |
| Total  | 135.0 mg |

The coatings given below were applied to the core tablets thus obtained to give enteric tablets. Undercoatings 1, 2 were applied with Highcoater (Freund Sangyo) at an air supply temperature of 70°C and an exhaust temperature of 40°C, at a pan revolution number of 13 rpm. The enteric coating was applied at an air supply temperature of 55°C and an exhaust temperature of 37°C.

|              |          |
|--------------|----------|
| Core tablets | 135.0 mg |
|--------------|----------|

Undercoating 1

|  |           |
|--|-----------|
| Hydroxypropylmethylcellulose                           | 1.4 mg    |
| Aluminum hydroxide-sodium<br>bicarbonate coprecipitate | 0.4 mg    |
| Talc   | 0.1 mg    |
| Purified water   | (23.0 mg) |
| Total  | 1.9 mg    |

Undercoating 2

|                              |        |
|------------------------------|--------|
| Hydroxypropylmethylcellulose | 3.1 mg |
| Titanium oxide               | 1.0 mg |

|  |           |
|--|-----------|
| Purified water                         | (56.0 mg) |
| Total                                  | 4.1 mg    |
| Enteric coating                        |           |
| Hydroxypropylmethylcellulose phthalate | 3.1 mg    |
| Cetanol                                | 0.2 mg    |
| Talc                                   | 0.2 mg    |
| Ethanol                                | (35.0 mg) |
| Purified water                         | (10.0 mg) |
| Total                                  | 3.5 mg    |
| Aggregate                              | 144.5 mg  |

With the enteric tablets of omeprazole thus obtained, dissolution rate in the 2nd fluid (pH: ca. 6.8) according to the Pharmacopoeia of Japan was determined after reservation under conditions of 25°C, 85% RH and 40°C, 82% RH respectively for 2 weeks. The results are shown in Fig. 6 and Fig. 7. As will be apparent from Figs. 6,7, the enteric tablets of this invention using aluminum hydroxide-sodium bicarbonate coprecipitate and the buffer agent (sodium pyrophosphate) exhibited persistently a good dissolution property after preservation under a humidified condition at a high temperature as well as immediately after preparation.

#### Example 2-3

Enteric tablets of omeprazole of the composition given below are produced according to the method of Example 2-2.

#### Core tablets

|  |         |
|--|---------|
| Omeprazole   | 20.0 mg |
| Aluminum hydroxide-sodium<br>bicarbonate coprecipitate | 13.0 mg |
| Sodium pyrophosphate                                   | 2.0 mg  |

|  |           |
|--|-----------|
| Lactose  | 83.0 mg   |
| Sodium carboxymethylstarch                             | 8.0 mg    |
| Sodium laurylsulfate                                   | 0.3 mg    |
| Hydroxypropylcellulose                                 | 1.0 mg    |
| Magnesium stearate                                     | 0.5 mg    |
| Total  | 135.0 mg  |
| Undercoating 1   |           |
| Hydroxypropylmethylcellulose                           | 1.4 mg    |
| Aluminum hydroxide-sodium<br>bicarbonate coprecipitate | 0.4 mg    |
| Talc   | 0.1 mg    |
| Purified water   | (23.0 mg) |
| Total  | 1.9 mg    |
| Undercoating 2   |           |
| Hydroxypropylmethylcellulose                           | 3.1 mg    |
| Titanium oxide   | 1.0 mg    |
| Purified water   | (56.0 mg) |
| Total  | 4.1 mg    |
| Enteric coating  |           |
| Hydroxypropylmethylcellulose phthalate                 | 3.1 mg    |
| Cetanol  | 0.2 mg    |
| Talc   | 0.2 mg    |
| Ethanol  | (35.0 mg) |
| Purified water   | (10.0 mg) |
| Total  | 3.5 mg    |
| Aggregate  | 144.0 mg  |

Stability test and dissolution test were performed with the enteric tablets of omeprazole thus obtained, under preservation, and as a result, a good preservation stability and

a high dissolution rate were attained.

#### Experimental Example 3-1

A quantity of 100 mg of omeprazole, aluminum glycinate and disodium hydrogenphosphate as a buffer were dispersed in 20 ml of water and preserved at 25°C. The resulting white suspension was observed of the appearance change with the lapse of day.

Control solutions containing no aluminum glycinate and no buffer, respectively were also prepared and observed of the change in appearance at 25°C with the lapse of day.

Table 3-1

|                            | Substance added                                       |   | mg  | Change in appearance at 25°C |                   |                    |
|----------------------------|---|---|-----|------------------------------|-------------------|--------------------|
|                            |   |   |     | 1 day                        | 3 day             | 7 day              |
| THE<br>IN-<br>VEN-<br>TION | Aluminum glycinate                                    |   | 100 | white                        | white             | white              |
|                            | Na <sub>2</sub> HPO <sub>4</sub> • 12H <sub>2</sub> O |   | 30  |                              |                   |                    |
|                            | Aluminum glycinate                                    |   | 100 | white                        | white             | white              |
|                            | Na <sub>2</sub> HPO <sub>4</sub> • 12H <sub>2</sub> O |   | 100 |                              |                   |                    |
|                            | None  |   | -   | pale<br>violet               | violet            | blackish<br>violet |
| CON-<br><br>TROL           | Ant-<br>acid  | Aluminum<br>glycinate                                 | 200 | slightly<br>violet           | brown             | brown              |
|                            |   | Aluminum<br>hydroxide                                 | 200 | violet                       | violet            | violet             |
|                            |   | Magnesium<br>carbonate                                | 200 | white                        | Slightly<br>brown | pale<br>brown      |
|                            |   | Synthetic<br>hydrotalcite                             | 200 | white                        | Slightly<br>gray  | pale<br>brown      |
|                            | Bu-<br>ffer   | Na <sub>2</sub> HPO <sub>4</sub> • 12H <sub>2</sub> O | 200 | pale<br>brown                | pale<br>brown     | pale<br>brown      |
|                            |   | Sodium tartarate                                      | 200 | pale<br>violet               | violet            | violet             |
|                            |   | Sodium acetate  | 200 | slightly<br>brown            | pale<br>violet    | pale<br>violet     |
|                            |   | Sodium<br>bicarbonatete                               | 200 | white                        | slightly<br>brown | pale<br>violet     |
|                            |   | Sodium<br>polyphosphate                               | 200 | slightly<br>brown            | slightly<br>brown | pale<br>brown      |
|                            |   | Dipotassium<br>hydrogenphospahte                      | 200 | pale<br>brown                | pale<br>brown     | pale<br>brown      |

From the results above, it is apparent that the conjoint use of aluminum glycinate and a buffer does not discolor omeprazole as compared with single use of aluminum glycinate or

a buffer alone, and accordingly, stabilizes omeprazole.

#### Example 3-1

The composition mentioned below was charged into a kneader for mixing for about 20 minutes, kneaded by adding an appropriate amount of purified water, granulated on an extrusion granulator (screen diameter of 1.0 mm), and made into spherical granules with the aid of Marumerizer (Fuji Powder Co.). The granules thus obtained were dried in a fluidized bed drier at an air feed temperature of 50 °C for 30 minutes and filtered through a sieve to give granules of 14~24 meshes.

|  |         |
|--|---------|
| Omeprazole                             | 5.0 mg  |
| Aluminum glycinate                     | 5.0 mg  |
| Sodium pyrophosphate                   | 2.0 mg  |
| Crystalline cellulose                  | 4.0 mg  |
| Low substituted hydroxypropylcellulose | 4.0 mg  |
| Hydroxypropylcellulose                 | 0.5 mg  |
| Mannitol                               | 54.5 mg |
| Total                                  | 75.0 mg |

#### Example 3-2

The composition given below was made into granules according to Example 3-1. Of the composition, disodium hydrogenphosphate was incorporated by dissolving it in purified water.

|   |        |
|---|--------|
| Omeprazole  | 5.0 mg |
| Aluminum glycinate                                    | 5.0 mg |
| Na <sub>2</sub> HPO <sub>4</sub> · 12H <sub>2</sub> O | 1.5 mg |
| Crystalline cellulose                                 | 4.0 mg |
| Low substituted hydroxypropylcellulose                | 4.0 mg |



|                        |         |
|------------------------|---------|
| Hydroxypropylcellulose | 0.5 mg  |
| Mannitol               | 55.0 mg |
| Total                  | 75.0 mg |

## Example 3-3

The granules obtained in Example 3-2 were applied with the coatings given below to give enteric granules. Undercoatings 1 and 2 were applied in a fluidized spray drier (Okawara Co.) at an air feed temperature of 75°C and an exhaust temperature of 55°C whereas Enteric coating was applied in the same drier at an air feed temperature of 65°C and an exhaust temperature of 50°C.

The granules in Example 3-2 75.0 mg

## Undercoating 1

|   |           |
|---|-----------|
| Hydroxypropylmethylcellulose                          | 3.5 mg    |
| Aluminum glycinate                                    | 1.4 mg    |
| Na <sub>2</sub> HPO <sub>4</sub> · 12H <sub>2</sub> O | 0.1 mg    |
| Talc  | 0.5 mg    |
| Purified water  | (64.5 mg) |
| Total   | 5.5 mg    |

## Undercoating 2

|                              |           |
|------------------------------|-----------|
| Hydroxypropylmethylcellulose | 3.5 mg    |
| Titanium oxide               | 2.5 mg    |
| Talc                         | 0.5 mg    |
| Purified water               | (64.5 mg) |
| Total                        | 6.5 mg    |

## Enteric coating

|  |         |
|--|---------|
| Hydroxypropylmethylcellulose phthalate | 10.7 mg |
| Cetanol                                | 0.5 mg  |

|                    |           |
|--------------------|-----------|
| Talc               | 1.8 mg    |
| Methylene chloride | (33.0 mg) |
| Ethanol            | (86.0 mg) |
| Purified water     | (33.0 mg) |
| Total              | 13.0 mg   |

The enteric granules of omeprazole thus obtained had a good dissolution property and were stable after preservation under heating or humidifying conditions.

#### Example 3-4

Of the composition given below, omeprazole, aluminum glycinate, mannitol,  $\alpha$ -starch, sodium laurylsulfate and hydroxypropylcellulose were homogeneously mixed, and to the mixture, an appropriate amount of purified water dissolving therein sodium pyrophosphate was added to carry out kneading, followed by drying in a fluidized drier at 50°C for 30 minutes.

The dried granules thus obtained were passed through a sieve of 24 mesh and added and mingled with magnesium stearate. Then the granules were made into tablets (core) of 135 mg per one tablet by means of a rotary tableting machine.

|                        |          |
|------------------------|----------|
| Omeprazole             | 20.0 mg  |
| Aluminum glycinate     | 20.0 mg  |
| Sodium pyrophosphate   | 1.0 mg   |
| Mannitol               | 71.7 mg  |
| $\alpha$ -Starch       | 20.0 mg  |
| Sodium laurylsulfate   | 0.3 mg   |
| Hydroxypropylcellulose | 1.0 mg   |
| Magnesium stearate     | 1.0 mg   |
| Total                  | 135.0 mg |

## Example 3-5

The tablets (core) obtained in Example 3-4 were applied with coatings of the compositions given below to give enteric tablets. Undercoatings 1 and 2 were applied with High-coater (Freund Sangyo Co.) at an air feed temperature of 70°C and an exhaust temperature of 40°C, at a pan revolution number of 13 rpm. Enteric coating was applied with the same device at an air feed temperature of 55°C and an exhaust temperature of 37°C.

Tablets of Example 3-4 135.0 mg

## Undercoating 1

|   |           |
|---|-----------|
| Hydroxypropylcellulose                                | 1.5 mg    |
| Aluminum glycinate                                    | 0.35mg    |
| Na <sub>2</sub> HPO <sub>4</sub> · 12H <sub>2</sub> O | 0.05mg    |
| Purified water  | (23.0 mg) |
| Total   | 1.9 mg    |

## Undercoating 2

|                        |           |
|------------------------|-----------|
| Hydroxypropylcellulose | 3.1 mg    |
| Titanium oxide         | 1.0 mg    |
| Purified water         | (56.0 mg) |
| Total                  | 4.1 mg    |

## Enteric coating

|  |           |
|--|-----------|
| Hydroxypropylmethylcellulose phthalate | 3.1 mg    |
| Cetanol                                | 0.2 mg    |
| Talc                                   | 0.2 mg    |
| Ethanol                                | (35.0 mg) |
| Purified water                         | (10.0 mg) |
| Total                                  | 3.5 mg    |

## Aggregate

144.5 mg

## Example 3-6

Core granules of the composition given below were produced according to Example 3-1. The sodium pyrophosphate used was incorporated by dissolving it in purified water. In order to prevent an adverse effect of proton released from the enteric film upon omeprazole, aluminum glycinate and  $\text{Na}_2\text{HPO}_4 \cdot 12\text{H}_2\text{O}$  were incorporated in Undercoating 1. Coating was conducted by the use of a fluidized bed drier (Okawara Co.). Undercoatings 1 and 2 were applied at an air feed temperature of 75°C, an exhaust temperature of 55°C and Enteric coating was likewise applied at an air feed temperature of 55°C and an exhaust temperature of 40°C.

## Core granules

|  |         |
|--|---------|
| Omeprazole                             | 5.0 mg  |
| Aluminum glycinate                     | 10.0 mg |
| Sodium pyrophosphate                   | 2.0 mg  |
| Crystalline cellulose                  | 4.0 mg  |
| Low substituted hydroxypropylcellulose | 4.0 mg  |
| Hydroxypropylcellulose                 | 0.5 mg  |
| Mannitol                               | 44.5 mg |
| Total                                  | 70.0 mg |

## Undercoating 1

|  |           |
|--|-----------|
| Hydroxypropylcellulose                               | 3.2 mg    |
| Aluminum glycinate                                   | 1.2 mg    |
| $\text{Na}_2\text{HPO}_4 \cdot 12\text{H}_2\text{O}$ | 0.1 mg    |
| Talc   | 0.5 mg    |
| Purified water                                       | (60.0 mg) |

|   |           |
|---|-----------|
| Total                                   | 5.0 mg    |
| Undercoating 2                          |           |
| Hydroxypropylmethylcellulose            | 3.5 mg    |
| Titanium oxide                          | 1.0 mg    |
| Talc                                    | 0.5 mg    |
| Purified water                          | (65.0 mg) |
| Total                                   | 5.0 mg    |
| Enteric coating                         |           |
| Methacrylic acid/acrylic acid copolymer |           |
| (solid content)                         | 15.0 mg   |
| Polyethylene glycol 6000                | 1.3 mg    |
| Tween 80                                | 0.7 mg    |
| Talc                                    | 3.0 mg    |
| Purified water                          | (50.0 mg) |
| Total                                   | 20.0 mg   |

## Reference Example 3-1

Tablets (core tablets) were produced from the composition given below according to Example 3-4.

|                        |          |
|------------------------|----------|
| Omeprazole             | 20.0 mg  |
| Mannitol               | 13.2 mg  |
| $\alpha$ -Starch       | 20.0 mg  |
| Sodium laurylsulfate   | 0.3 mg   |
| Hydroxypropylcellulose | 1.0 mg   |
| Magnesium stearate     | 0.5 mg   |
| Total                  | 135.0 mg |

To the tablets (core tablets) obtained were applied Undercoating 2 and Enteric coating applied in Example 3-5 to give enteric tablets.

## Reference Example 3-2

The composition of the formulation given below was made into tablets (core tablets) according to Example 3-4.

|                        |          |
|------------------------|----------|
| Omeprazole             | 20.0 mg  |
| Aluminum glycinate     | 20.0 mg  |
| Mannitol               | 73.2 mg  |
| $\alpha$ -Starch       | 21.0 mg  |
| Sodium laurylsulfate   | 0.3 mg   |
| Hydroxypropylcellulose | 1.0 mg   |
| Magnesium stearate     | 0.5 mg   |
| Total                  | 135.0 mg |

The tablets (core tablets) thus obtained were applied with the film coatings in Example 3-5 to yield enteric tablets.

## Experimental Example 3-2

The core tablets obtained in Example 3-4, the enteric tablets in Example 3-5, the core tablets and enteric tablets in Reference Example 3-1 and the core tablets and enteric tablets in Reference Example 3-2 were respectively placed in a glass bottle, and allowed to stand for 2 weeks with the bottles sealingly stoppered under 60°C condition and opened under 40 °C, 75% RH conditions, respectively. The results obtained of the change in appearance are shown in Table 3-2.

Table 3-2

|                                 | As prepared    | Sealingly stoppered at 60°C | Opened at 40°C 75% RH |
|---------------------------------|----------------|-----------------------------|-----------------------|
| Example 3-4 (core tablets)      | white          | white                       | white                 |
| Example 3-5 (enteric tablets)   | white          | white                       | white                 |
| Ref. Example 3-1 (core tablets) | slightly brown | pale brown                  | pale brown            |
| ditto (enteric tablets)         | white          | slightly brown              | pale brown            |
| Ref. Example 3-2 (core tablets) | pale brown     | pale brown                  | pale brown            |
| ditto (enteric tablets)         | slightly brown | pale brown                  | pale brown            |

As will be apparent from the results in Table 3-2, the change in appearance was significantly improved by incorporating aluminum glycinate and a buffer.

#### Experimental Example 3-3

Tablets (core tablets) were produced in the formulation given below according to Example 3-4 (Sample A).

|   |          |
|---|----------|
| Omeprazole  | 20.0 mg  |
| Aluminum glycinate                                    | 10.0 mg  |
| sodium pyrophosphate                                  | 10.0 mg  |
| Na <sub>2</sub> HPO <sub>4</sub> · 12H <sub>2</sub> O | 2.0 mg   |
| Mannitol  | 87.5 mg  |
| Carboxymethylcellulose                                | 10.0 mg  |
| Magnesium stearate                                    | 0.5 mg   |
| Total   | 130.0 mg |

Tablets (core tablets) containing no stabilizer were produced in the formulation given below according to Example 3-4 (Control A).

|                        |          |
|------------------------|----------|
| Omeprazole             | 20.0 mg  |
| Mannitol               | 99.5 mg  |
| Carboxymethylcellulose | 10.0 mg  |
| Magnesium stearate     | 0.5 mg   |
| Total                  | 130.0 mg |

Sample A and Control A were preserved under 40°C, 75% RH conditions for 4 weeks and then measured of change in appearance with a colorimeter to determine  $\Delta E$  values. The results obtained are shown below.

| Preparation | $\Delta E$ |
|-------------|------------|
| Sample A    | 7.0        |
| Control A   | 14.0       |

As will be apparent from the experimental results, in case where aluminum glycinate or a buffer alone is incorporated in omeprazole no stabilization effect was attained whereas the conjoint use of both can stabilize significantly omeprazole, and accordingly, a stabilized preparation containing antiulcer agent was obtained.

#### Experimental Example 4-1

A quantity of 100 mg of omeprazole, 100 mg of various amino acid and 100 mg of disodium hydrogenphosphate as a buffer were dispersed in 20 ml of water and preserved at 25°C. The resulting white suspension was observed of the appearance change with the lapse of day.

Control solutions containing no amino acid and no buffer, respectively were also prepared and observed of the change in appearance at 25°C with the lapse of day.



Table 3-1

|                            | Substance added                                       |   | mg  | Change in appearance at 25°C |                   |                    |
|----------------------------|---|---|-----|------------------------------|-------------------|--------------------|
|                            |   |   |     | 1 day                        | 3 days            | 7 days             |
| THE<br>IN-<br>VEN-<br>TION | Glycine   |   | 100 |                              |                   |                    |
|                            | Na <sub>2</sub> HPO <sub>4</sub> · 12H <sub>2</sub> O |   | 100 | white                        | white             | white              |
|                            | L-Isoleucine  |   | 100 |                              |                   |                    |
|                            | Na <sub>2</sub> HPO <sub>4</sub> · 12H <sub>2</sub> O |   | 100 | white                        | white             | white              |
|                            | L-Alanine   |   | 100 | white                        | white             | gray               |
|                            | Na <sub>2</sub> HPO <sub>4</sub> · 12H <sub>2</sub> O |   | 100 |                              |                   |                    |
|                            | L-Threonine   |   | 100 | white                        | white             | gray               |
|                            | Na <sub>2</sub> HPO <sub>4</sub> · 12H <sub>2</sub> O |   | 100 |                              |                   |                    |
|                            | L-Phenylalanine                                       |   | 100 | white                        | white             | gray               |
|                            | Na <sub>2</sub> HPO <sub>4</sub> · 12H <sub>2</sub> O |   | 100 |                              |                   |                    |
| CON-<br>TROL               | None  |   | -   | pale<br>violet               | violet            | blackish<br>violet |
|                            | Amino<br>acid   | Glycine   | 100 | violet                       | violet            | blackish<br>violet |
|                            |   | L-Alanine   | 100 | pale<br>violet               | violet            | blackish<br>violet |
|                            |   | L-Isoleucine  | 100 | slightly<br>brown            | violet            | blackish<br>violet |
|                            | Bu-<br>ffer   | Na <sub>2</sub> HPO <sub>4</sub> · 12H <sub>2</sub> O | 200 | pale<br>brown                | pale<br>brown     | pale<br>brown      |
|                            |   | Sodium tartarate                                      | 200 | pale<br>violet               | violet            | violet             |
|                            |   | Sodium<br>pyrophosphate                               | 200 | slightly<br>brown            | slightly<br>brown | pale<br>brown      |
|                            |   | Sodium<br>acetate                                     | 200 | slightly<br>brown            | pale<br>violet    | pale<br>violet     |
|                            |   | Sodium<br>bicarbonate                                 | 200 | white                        | slightly<br>brown | pale<br>violet     |

|  |                               |     |                |                |            |
|--|-------------------------------|-----|----------------|----------------|------------|
|  | Sodium polyphosphate          | 200 | slightly brown | slightly brown | pale brown |
|  | Dipotassium hydrogenphosphate | 200 | pale brown     | pale brown     | pale brown |
|  | Magnesium carbonate           | 200 | white          | slightly brown | pale brown |

From the results above, it is apparent that the conjoint use of an amino acid and a buffer does not discolor omeprazole as compared with single use of an amino acid or a buffer alone, and accordingly, stabilizes omeprazole.

#### Example 4-1

Of the composition given below, omeprazole, crystalline cellulose, low substituted hydroxypropylcellulose, hydroxypropylcellulose and mannitol were charged into a kneader and mixed for ca. 20 minutes. An appropriate amount of purified water dissolving therein glycine and disodium hydrogenphosphate was further added and kneaded. The resulting mixture was dried in a fluidized drier at 50°C for 30 minutes. Thereafter, granules of 14~24 meshes were obtained by the use of a sieve.

|   |         |
|---|---------|
| Omeprazole  | 5.0 mg  |
| Glycine   | 2.5 mg  |
| Na <sub>2</sub> HPO <sub>4</sub> · 12H <sub>2</sub> O | 2.5 mg  |
| Crystalline cellulose                                 | 4.0 mg  |
| Low substituted hydroxypropylcellulose                | 4.0 mg  |
| Hydroxypropylcellulose                                | 0.5 mg  |
| Mannitol  | 56.5 mg |
| Total   | 75.0 mg |

#### Example 4-2

The composition of the formulation given below was made

into granules according to Example 4-1. The sodium L-glutamate and sodium pyrophosphate dissolved in purified water were incorporated.

|  |         |
|--|---------|
| Omeprazole                             | 5.0 mg  |
| Sodium L-glutamate                     | 2.5 mg  |
| Sodium pyrophosphate                   | 1.0 mg  |
| Crystalline cellulose                  | 4.0 mg  |
| Low substituted hydroxypropylcellulose | 4.0 mg  |
| Hydroxypropylcellulose                 | 0.5 mg  |
| Mannitol                               | 58.5 mg |
| Total                                  | 75.0 mg |

#### Example 4-3

From the composition given below, granules were produced according to Example 4-1. The L-alanine and dipotassium hydrogenphosphate were incorporated by dissolving them in purified water.

|  |         |
|--|---------|
| Omeprazole                             | 5.0 mg  |
| L-alanine                              | 1.5 mg  |
| K <sub>2</sub> HPO <sub>4</sub>        | 1.5 mg  |
| Crystalline cellulose                  | 4.0 mg  |
| Low substituted hydroxypropylcellulose | 4.0 mg  |
| Hydroxypropylcellulose                 | 0.5 mg  |
| Mannitol                               | 58.5 mg |
| Total                                  | 75.0 mg |

#### Example 4-4

The granules obtained in Example 4-3 were applied with coatings of the compositions given below to give enteric granules. Undercoatings 1, 2 were applied in a fluidized bed

drier (Okawara Co.) at an air feed temperature of 75°C and an exhaust temperature of 55°C and Enteric coating was applied similarly at an air feed temperature of 65°C and an exhaust temperature of 50°C.

Granules in Example 4-3 75.0 mg

Undercoating 1

|  |           |
|--|-----------|
| Hydroxypropylmethylcellulose phthalate | 3.5 mg    |
| Synthetic talcite                      | 1.5 mg    |
| Talc                                   | 0.5 mg    |
| Purified water                         | (64.5 mg) |
| Total                                  | 5.5 mg    |

Undercoating 2

|                              |           |
|------------------------------|-----------|
| Hydroxypropylmethylcellulose | 3.5 mg    |
| Titanium oxide               | 2.5 mg    |
| Talc                         | 0.5 mg    |
| Purified water               | (64.5 mg) |
| Total                        | 6.5 mg    |

Enteric coating

|                              |           |
|------------------------------|-----------|
| Hydroxypropylmethylcellulose | 10.7 mg   |
| Cetanol                      | 0.5 mg    |
| Talc                         | 1.8 mg    |
| Methylene chloride           | (33.0 mg) |
| Ethanol                      | (86.0 mg) |
| Purified water               | (33.0 mg) |
| Total                        | 13.0 mg   |
| Aggregate                    | 100.0 mg  |

Example 4-5

Of the composition given below, omeprazole, mannitol,

sodium carboxymethylstarch, sodium laurylsulfate and hydroxypropylcellulose were mixed uniformly. An appropriate amount of purified water dissolving therein L-isoleucine and sodium pyrophosphate was added to the mixture and kneaded together, and then dried in a fluidized drier at 50°C for 30 minutes. The dried particles were passed through a sieve of 24 mesh and mixed with magnesium stearate, and then produced into tablets (core tablets) of 135 mg per one tablet by means of a rotary tableting machine.

|                            |          |
|----------------------------|----------|
| Omeprazole                 | 20.0 mg  |
| L-Isoleucine               | 3.0 mg   |
| Sodium pyrophosphate       | 3.0 mg   |
| Mannitol                   | 99.2 mg  |
| Sodium carboxymethylstarch | 8.0 mg   |
| Sodium laurylsulfate       | 0.3 mg   |
| Hydroxypropylcellulose     | 1.0 mg   |
| Magnesium stearate         | 0.5 mg   |
| Total                      | 135.0 mg |

#### Example 4-6

The tablets (core tablets) obtained in Example 4-5 were applied with coatings of the compositions given below to yield enteric tablets. Undercoatings 1, 2 were applied by means of High-coater (Freund Sangyo Co.) at an air feed temperature of 70°C and an exhaust temperature of 40°C, at a pan revolution number of 13 rpm. Enteric coating was likewise applied at an air feed temperature of 55°C and an exhaust temperature of 37 °C.

|                        |          |
|------------------------|----------|
| Tablets in Example 4-5 | 135.0 mg |
|------------------------|----------|

## Undercoating 1

|  |           |
|--|-----------|
| Hydroxypropylmethylcellulose                           | 1.5 mg    |
| Aluminum hydroxide-sodium<br>bicarbonate coprecipitate | 0.4 mg    |
| Purified water   | (23.0 mg) |
| Total  | 1.9 mg    |

## Undercoating 2

|                              |           |
|------------------------------|-----------|
| Hydroxypropylmethylcellulose | 3.1 mg    |
| Titanium oxide               | 1.0 mg    |
| Purified water               | (56.0 mg) |
| Total                        | 4.1 mg    |

## Enteric coating

|  |           |
|--|-----------|
| Hydroxypropylmethylcellulose phthalate | 3.1 mg    |
| Cetanol                                | 0.2 mg    |
| Talc                                   | 0.2 mg    |
| Ethanol                                | (35.0 mg) |
| Purified water                         | (10.0 mg) |
| Total                                  | 3.5 mg    |
| Aggregate                              | 144.5 mg  |

## Example 4-7

Core granules were produced according to Example 4-1 from the composition given below. The glycine and sodium pyrophosphate as a stabilizer was incorporated by dissolving them in purified water. In order to prevent an adverse effect of proton released from the enteric film upon omeprazole, aluminum hydroxide •sodium bicarbonate coprecipitate and disodium hydrogenphosphate were incorporated. Coating was conducted by the use of a fluidized bed drier (Okawara Co.). Undercoatings 1 and 2 were applied at an air feed temperature

of 75°C and an exhaust temperature of 55°C while Enteric coating was applied at an air feed temperature of 55°C and an exhaust temperature of 40°C.

**Core granules**

|  |         |
|--|---------|
| Omeprazole                             | 5.0 mg  |
| Glycine                                | 2.0 mg  |
| Sodium pyrophosphate                   | 2.0 mg  |
| Crystalline cellulose                  | 4.0 mg  |
| Low substituted hydroxypropylcellulose | 4.0 mg  |
| Hydroxypropylcellulose                 | 0.5 mg  |
| Mannitol                               | 52.5 mg |
| Total                                  | 70.0 mg |

**Undercoating 1**

|  |           |
|--|-----------|
| Hydroxypropylmethylcellulose                           | 3.2 mg    |
| Aluminum hydroxide-sodium<br>bicarbonate coprecipitate | 1.2 mg    |
| Na <sub>2</sub> HPO <sub>4</sub> · 12H <sub>2</sub> O  | 0.1 mg    |
| Talc   | 0.5 mg    |
| Purified water   | (60.0 mg) |
| Total  | 5.0 mg    |

**Undercoating 2**

|                              |           |
|------------------------------|-----------|
| Hydroxypropylmethylcellulose | 3.5 mg    |
| Titanium oxide               | 1.0 mg    |
| Talc                         | 0.5 mg    |
| Purified water               | (65.0 mg) |
| Total                        | 5.0 mg    |

**Enteric coating**

|  |         |
|--|---------|
| Methacrylic acid/acrylic acid<br>copolymer (solid) | 15.0 mg |
|--|---------|

|                          |           |
|--------------------------|-----------|
| Polyethylene glycol 6000 | 1.3 mg    |
| Tween 80                 | 0.7 mg    |
| Talc                     | 3.0 mg    |
| Purified water           | (50.0 mg) |
| Total                    | 20.0 mg   |
| Aggregate                | 100.0 mg  |

## Experimental Example 4-2

Tablets (core tablets) were produced in the formulation given below according to Example 4-5 (Sample B).

|   |          |
|---|----------|
| Omeprazole  | 20.0 mg  |
| Glycine   | 10.0 mg  |
| Na <sub>2</sub> HPO <sub>4</sub> · 12H <sub>2</sub> O | 2.0 mg   |
| Mannitol  | 87.5 mg  |
| Carboxymethylcellulose                                | 10.0 mg  |
| Magnesium stearate                                    | 0.5 mg   |
| Total   | 130.0 mg |

Tablets (core) containing no stabilizer were produced in the formulation below according to Example 4-5 (Control B).

|                        |          |
|------------------------|----------|
| Omeprazol              | 20.0 mg  |
| Mannitol               | 99.5 mg  |
| Carboxymethylcellulose | 10.0 mg  |
| Magnesium stearate     | 0.5 mg   |
| Total                  | 130.0 mg |

Sample B and Control B were preserved under 40°C, 75% RH for 4 weeks and measured of the change in appearance with a colorimeter to determine ΔE values. The results obtained are shown below.



| <u>Preparation</u> | <u><math>\Delta E</math></u> |
|--------------------|------------------------------|
| Sample B           | 8.2                          |
| Control B          | 14.7                         |

As will be apparent from above, no stabilization effect was obtained when amino acid, an acid salt of an amino acid or an alkali salt of an amino acid or a buffer was singly incorporated in omeprazole but when the aforementioned amino acid or the like and the buffer are used in admixture, omeprazole were significantly stabilized, whereby a stabilized preparation containing an antiulcer agent was obtained.

[Industrial Applicability]

The pharmaceutical preparations of this invention exhibit a superior inhibitory activity to secretion of gastric acid and superior antiulcer activity and can be used for the treatment of digestive ulcers, etc. of human or other mammals.

## CLAIMS

1. An enteric pharmaceutical composition, containing antiulcer agent, improved in stability and unchanged in dissolution property with the lapse of time, which composition comprises a core portion including a 2-[(2-pyridyl)methylsulfinyl]-benzimidazole compound that has antiulcer activity and is unstable to acid, an undercoating of one or two layers covering the core portion and an enteric coating further covering the undercoating, wherein said core portion and/or said undercoating comprise a stabilizer selected from the group consisting of aluminum hydroxide • sodium bicarbonate coprecipitate alone, a mixture of the aforementioned coprecipitate and a buffer, a mixture of aluminum glycinate and a buffer, a mixture of an amino acid and a buffer, a mixture of an acid salt of an amino acid and a buffer, and a mixture of an alkali salt of an amino acid and a buffer.
2. An enteric pharmaceutical composition improved in stability and unchanged in dissolution property with the lapse of time, which composition comprises a core portion including a 2-[(2-pyridyl)methylsulfinyl] benzimidazole compound that has antiulcer activity and is unstable to an acid, an undercoating of one or two layers covering the core portion, and an enteric coating further covering the undercoating, wherein the core portion and/or the undercoating comprise aluminum hydroxide • sodium bicarbonate coprecipitate.
3. The enteric pharmaceutical composition as set forth in item 2, wherein the aluminum hydroxide • sodium bicarbonate coprecipitate in the undercoating is in the range of 0.01~10

parts by weight based on 100 parts by weight of the core portion.

4. The enteric pharmaceutical composition as set forth in item 2, wherein the undercoating comprises aluminum hydroxide · sodium bicarbonate coprecipitate and talc.

5. An enteric pharmaceutical composition improved in stability and unchanged in dissolution property with the lapse of time, which composition comprises a core portion including a 2-[(2-pyridyl)methylsulfinyl] benzimidazole compound that has antiulcer activity and is unstable to an acid, an undercoating of one or two layers covering the core portion, and an enteric coating further covering the undercoating, wherein the core portion and/or the undercoating comprise aluminum hydroxide · sodium bicarbonate coprecipitate and a buffer.

6. The enteric pharmaceutical composition as set forth in item 5, wherein the aluminum hydroxide · sodium bicarbonate coprecipitate and a buffer are in the range of, respectively, 0.01~0.5 part by weight and 0.01~2 parts by weight based on 1 part by weight of the 2-[(2-pyridyl)methylsulfinyl]-benzimidazole compound.

7. The enteric pharmaceutical composition as set forth in item 5, wherein the buffer is sodium tartarate, sodium acetate, sodium bicarbonate, sodium carbonate, sodium polyphosphate, potassium polyphosphate, sodium pyrophosphate, potassium pyrophosphate, disodium hydrogenphosphate, dipotassium hydrogenphosphate, trisodium phosphate or tripotassium phosphate.

8. An enteric pharmaceutical composition improved in stability

and unchanged in dissolution property with the lapse of time, which composition comprises a core portion including a 2-[(2-pyridyl)methylsulfinyl] benzimidazole compound that has antiulcer activity and is unstable to an acid, an undercoating of one or two layers covering the core portion, and an enteric coating further covering the undercoating, wherein the core portion and/or the undercoating comprise aluminum glycinate and a buffer.

9. The enteric pharmaceutical composition as set forth in item 8, wherein the aluminum glycinate and the buffer are in the range of, respectively, 0.1~2 parts by weight and 0.01~2 parts by weight based on 1 part by weight of the 2-[(2-pyridyl)methylsulfinyl] benzimidazole compound.

10. The enteric pharmaceutical composition as set forth in item 8, wherein the buffer is sodium tartarate, sodium acetate, sodium bicarbonate, sodium carbonate, sodium polyphosphate, potassium polyphosphate, sodium pyrophosphate, potassium pyrophosphate, disodium hydrogenphosphate, dipotassium hydrogenphosphate, trisodium phosphate or tripotassium phosphate.

11. An enteric pharmaceutical composition improved in stability and unchanged in dissolution property with the lapse of time, which composition comprises a core portion including a 2-[(2-pyridyl)methylsulfinyl] benzimidazole compound that has antiulcer activity and is unstable to an acid, an undercoating of one or two layers covering the core portion, and an enteric coating further covering the undercoating, wherein the core portion and/or the undercoating comprise a mixture of an amino

acid, an acid salt of an amino acid or an alkali salt of an amino acid and a buffer.

12. The enteric pharmaceutical composition as set forth in item 11, wherein the amino acid, acid salt of an amino acid, or alkali salt of an amino acid is in the range of 0.01~2 parts by weight and the buffer is in the range of 0.01~2 parts by weight, respectively, based on 1 part by weight of the 2-[(2-pyridyl)methylsulfinyl] benzimidazole compound.

13. The enteric pharmaceutical composition as set forth in item 11, wherein the amino acid, acid salt of an amino acid or alkali salt of an amino acid is glycine, glycine hydrochloride, L-alanine, DL-alanine, L-threonin, DL-threonin, L-isoleucine, L-valine, L-phenylalanine, L-glutamic acid, L-glutamic acid hydrochloride, sodium L-glutamate, L-asparagic acid, sodium L-asparagate, L-lysine or L-lysine-L-glutamate; and the buffer is an alkaline metal salt of phosphoric acid, sodium tartarate, sodium acetate, sodium bicarbonate, sodium polyphosphate, sodium pyrophosphate, potassium metaphosphate, magnesium oxide, magnesium hydroxide, magnesium carbonate, magnesium silicate or calcium carbonate.

14. The enteric pharmaceutical composition as set forth in item 11, wherein the amino acid, acid salt of an amino acid or alkali salt of an amino acid is glycine, L-alanine, DL-alanine or sodium L-glutamate; and the buffer is disodium hydrogenphosphate.

## DRAWINGS

Fig. 1

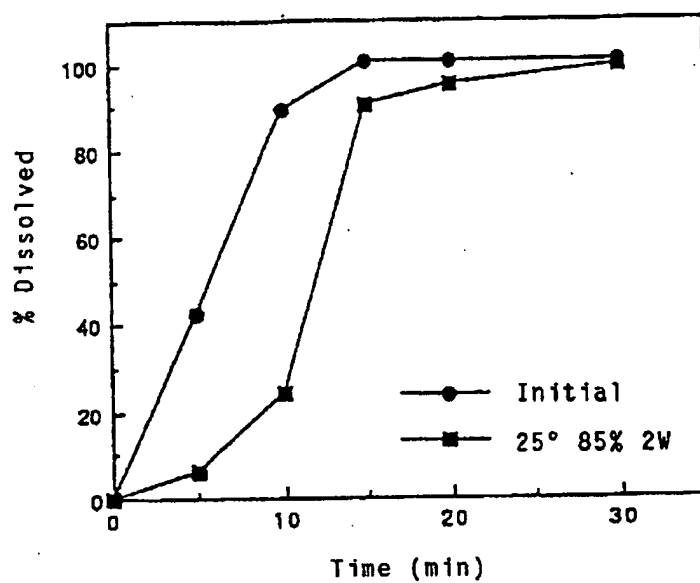


Fig. 2

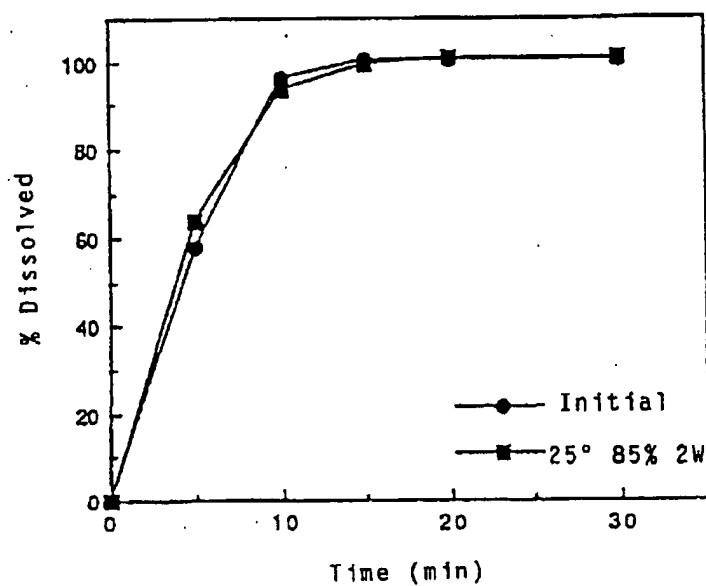


Fig. 3

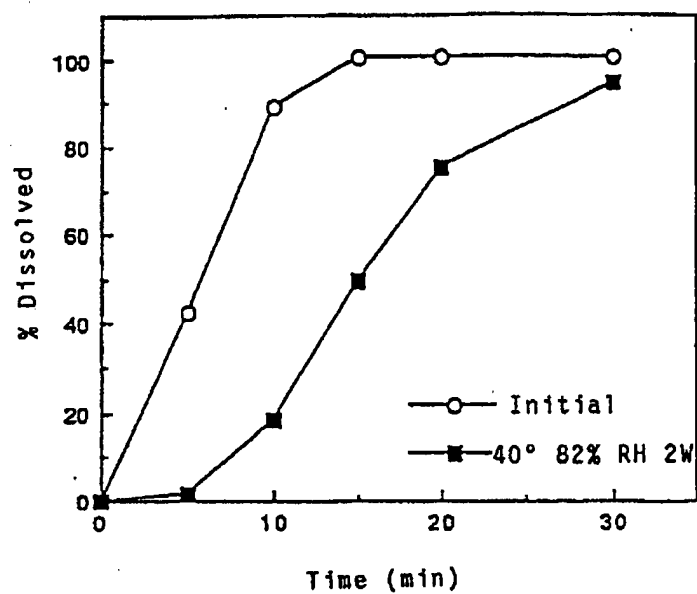


Fig. 4

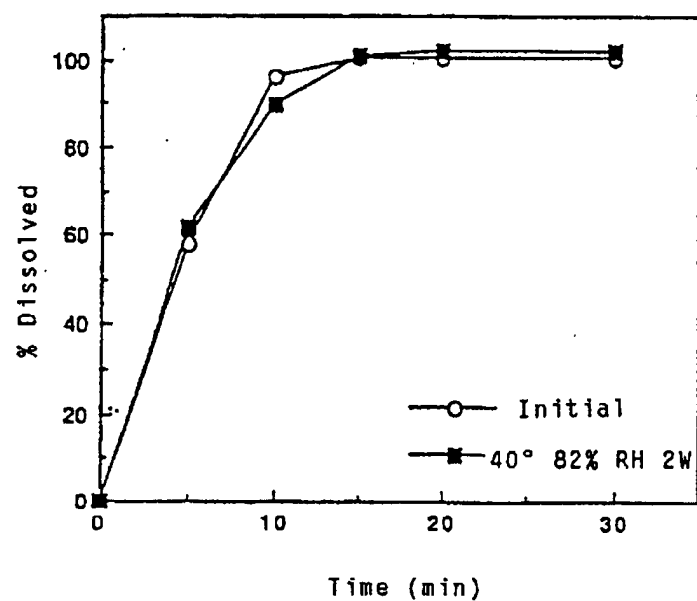
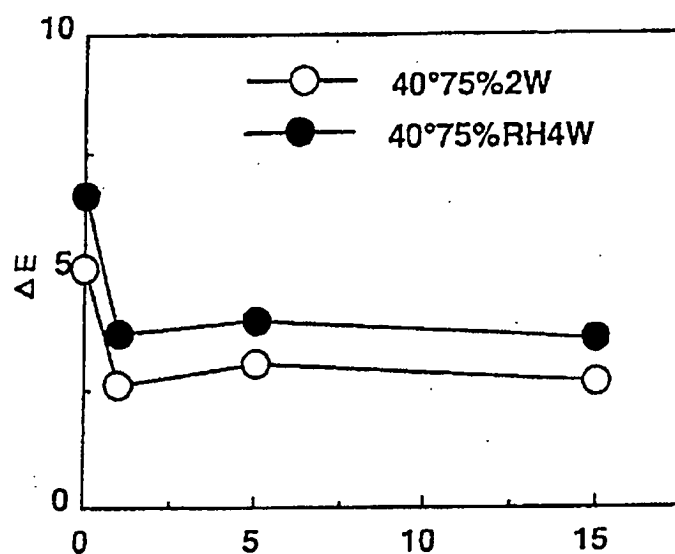


Fig. 5



additive amount of aluminum hydroxide-sodium  
bicarbonate coprecipitate (mg/135 mg)



Fig. 6

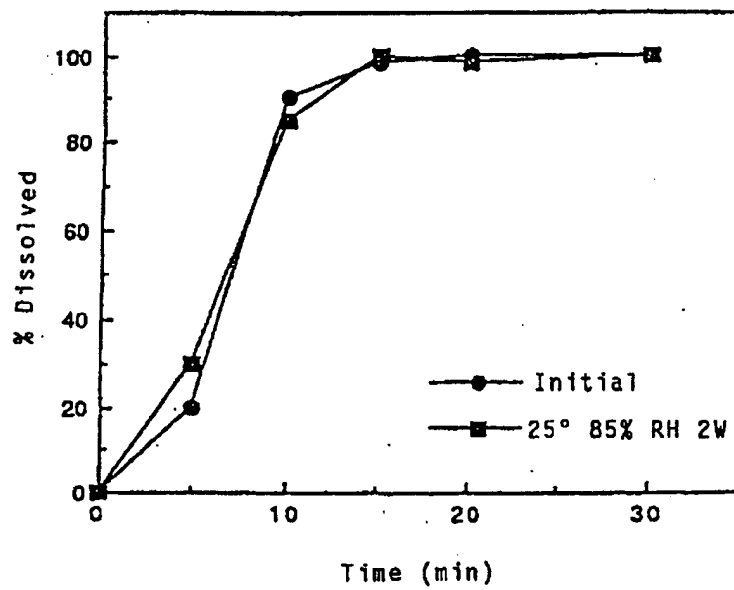
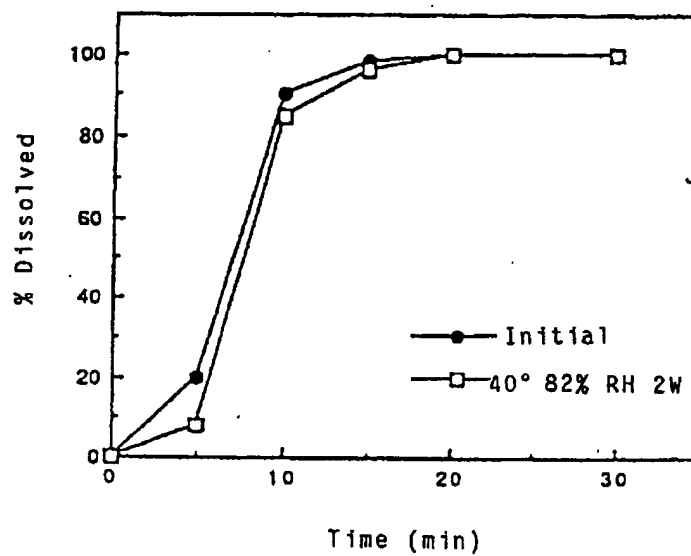


Fig. 7



## INTERNATIONAL SEARCH REPORT

PCT/JP 93/00920

International Application No

|  |  |                                     |
|--|--|-------------------------------------|
| <b>I. CLASSIFICATION OF SUBJECT MATTER</b> (If several classification symbols apply, indicate all) <sup>6</sup>  |  |                                     |
| According to International Patent Classification (IPC) or to both National Classification and IPC  |  |                                     |
| Int.Cl. 5 A61K31/44; A61K9/28; A61K9/50  |  |                                     |
| <b>II. FIELDS SEARCHED</b>   |  |                                     |
| Minimum Documentation Searched <sup>7</sup>  |  |                                     |
| Classification System  | Classification Symbols   |                                     |
| Int.Cl. 5  | A61K   |                                     |
| Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched <sup>8</sup>   |  |                                     |
| <b>III. DOCUMENTS CONSIDERED TO BE RELEVANT<sup>9</sup></b>  |  |                                     |
| Category <sup>10</sup>   | Citation of Document, <sup>11</sup> with indication, where appropriate, of the relevant passages <sup>12</sup>                                     | Relevant to Claim No. <sup>13</sup> |
| Y  | EP,A,0 248 634 (NIPPON CHEMIPHAR CO. LTD.)<br>9 December 1987<br>cited in the application<br>see page 5, line 35 - page 6, line 23;<br>claims 1-23 | 1-14                                |
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| <sup>10</sup> Special categories of cited documents :<br><sup>"A"</sup> document defining the general state of the art which is not considered to be of particular relevance<br><sup>"E"</sup> earlier document but published on or after the international filing date<br><sup>"L"</sup> document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)<br><sup>"O"</sup> document referring to an oral disclosure, use, exhibition or other means<br><sup>"P"</sup> document published prior to the international filing date but later than the priority date claimed<br><sup>"T"</sup> later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention<br><sup>"X"</sup> document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step<br><sup>"Y"</sup> document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art<br><sup>"A"</sup> document member of the same patent family |  |                                     |
| <b>IV. CERTIFICATION</b>   |  |                                     |
| Date of the Actual Completion of the International Search  | Date of Mailing of this International Search Report  |                                     |
| 13 MND_NAME 1993   | 28. 10. 93   |                                     |
| International Searching Authority  | Signature of Authorized Officer  |                                     |
| EUROPEAN PATENT OFFICE   | TZSCHOPPE D. A.  |                                     |

| III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET) |  |                       |
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| Y  | ES,A,2 024 993 (CENTRO GENESIS PARA LA INVESTIGACION S.L.)<br>1 March 1992<br>see the whole document<br>---  | 1-14                  |
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ON INTERNATIONAL PATENT APPLICATION NO.**

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This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.  
The members are as contained in the European Patent Office EDP file on  
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information. 13/10/93

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